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Die Deutsche Gesellschaft für innere Medizin hält ihre 54. Tagung von Montag, den 11. bis Donnerstag, den 14. Oktober 1943 in Wien unter dem Vorsitz von Herrn Prof. Dr. Eppinger-Wien ab.

Dieselbe ist als Kriegstagung geplant, es kommen dementsprechend vorwiegend nur kriegswichtige Themen zur Besprechung. Bisher sind folgende Vorträge und Referate vorgesehen:

I. Montag, den 11. Oktober 1943 *Kriegsseuchen.*

II. Dienstag, den 12. Oktober 1943

Vormittags: *Feldnephritis.*

Nachmittags: *Infektiöse Erkrankungen des Zentralnervensystems.*

III. Mittwoch, den 13. Oktober 1943

Vormittags: *Hepatitis epidemica.*

Nachmittags: *Freie Vorträge.*

IV. Donnerstag, den 14. Oktober 1943

Vormittags: *Das Ulcus ventriculi und duodeni und seine Behandlung unter dem Gesichtspunkt der Wehreinsatzfähigkeit.*

Die Namen der Referenten werden später bekanntgegeben. Vortragsmeldungen können nur in sehr beschränktem Umfang angenommen werden und sind mit Manuskript bis zum 25. August 1943 an den derzeitigen Vorsitzenden Herrn Professor Dr. Eppinger-Wien, Lazarettgasse 14 I, Medizinische Klinik, zu richten.

From the Medical Department of the Copenhagen County Hospital
(Director: Chief Physician Ferd. Wulff, M. D.).

On the Agglutination of the Blood Platelets under Normal and Pathological Conditions.

By

E. ØLLGAARD.

(Submitted for publication April 27, 1943).

In the older literature, the blood platelets were described as viscid formations, which was a mistake, however, for in citrated or otherwise stabilised blood they may be kept in suspension for a long time without agglutinating, and sedimented blood platelets just as sedimented erythrocytes can be restored to suspension by shaking. However, from the counting of blood platelets in undiluted citrate plasma it is known that a more or less pronounced spontaneous agglutination occurs, if there is the slightest impureness in glass or counting-cell, but even if there is not, the blood platelets of certain patients will nevertheless agglutinate, thus rendering it impossible to count them. On the other hand, if there is a question of blood without addition of anticoagulants, the platelets will be found to be the first to agglutinate on the appearance of coagulation. According to Lenggenhagen, the agglutination of the blood platelets is due to their being covered with a layer of freshly sedimented fibrin, which renders them viscid. Knowing that the primary nucleus in the venous thrombus is a conglomeration of blood platelets, the thrombotic process according to Lenggenhagen commences by the blood plates covering themselves with a membrane of absorbed fibrin, thus giving rise to coalescence of such platelets. These platelet agglutinates being heavier than normal blood plate-

lets, they will very rapidly sink down in the slow flow of blood, whereas, in patients with rapid blood perfusion, they will get no opportunity of sedimentation. Accordingly, two factors must be reckoned with as causes of spontaneous thrombosis, namely, reduced blood perfusion, and a change of the blood giving rise to agglutination of the blood plates; however, the reduced blood perfusion alone not being able to cause this platelet agglutination, the essential point to be studied in the pathogenesis of spontaneous venous thrombosis must be, what factors do give rise to this agglutination.

As was mentioned, Lenggenghagen assumes that it is due to fibrin formation caused by liberated thrombin, whereas other investigators assume a chemical or physico-chemical change in the blood, which according to Starlinger & Sametnik, Stuber & Lang causes discharge of the negatively charged platelets, according to Tannenberg, gives rise to processes which are analogous to those causing agglutination of the erythrocytes.

Thus, endeavours have not been wanting to solve this question with the help of methods appropriated for the study of agglutination of the blood platelets *in vitro*, either in plasma with the addition of calcium-sedimenting substances (Heusser, Starlinger & Sametnik, Stuber & Lang), or in native blood (Morawitz & Jürgens, Horwitz, Tannenberg). By these investigations it was found that the agglutinating tendency of the platelets varied from individual to individual, and that a considerable increase of the agglutinability is met with under certain pathological conditions. The methods requiring native blood are difficult to work with, however, affording, perhaps, sooner a measure for the total coagulation mechanism than for the first phase, the agglutination of the platelets, the other methods requiring plasma are easier to use but their value is detracted from by the drawback that spontaneous agglutination never is excluded.

Now, Øllgaard has shown that this tendency to spontaneous agglutination may be inhibited, if the blood, prior to counting the blood platelets in undiluted plasma *a. m.* Thomsen, is allowed to stand for 2 hours on a thermal water bath of 42° instead of in room temperature. When this thermal influence was used in counting the blood plates of blood samples drawn in a manner that spontaneous agglutination could be anticipated, the agglutination failed to occur, whereas a similar blood sample which had sedimented at 18°,

presented strong agglutination. At the same time it was shown that a temperature below 39° was without effect, and that the number of platelets was found to be the same at 18° and 42° even after 3 hours' standing and the blood plates acquired a regular, round shape.

This procedure thus enables one to get a perfectly stable suspension of blood plates in citrated plasma in which their agglutination can be examined without risk of eventual spontaneous agglutination. On addition of small quantities of mercury cyanide, mercury chloride and saponin to such thermally treated citrate plasma, distinct agglutination of the platelets ensued. Whereas these three substances do not cause agglutination in platelet-containing citrate plasma from blood which has sedimented at room temperature, they will give rise not only to microscopical but also to strong macroscopical agglutination in thermally treated plasma.

These three substances were found by experiments with a number of different agents. Among the substances which failed to give agglutination shall be mentioned tissue extract (aqueous extract of human brain) and lanthanum nitrate. The latter was by Starlinger-Sametnik used for discharging the negative platelets so that a microscopical agglutination ensued, but in the thermally treated citrate plasma, no macroscopical agglutination appeared even in concentrations which gave incipient sedimentation of protein substances.

The method of causing agglutination of the blood platelets is the same for all three substances. Citrate blood (1: 10) is placed on a thermal water bath of 42° for 3 hours; then all the supernatant plasma is pipetted off, and to 0.5 cm^3 of it is added 0.05 cm^3 of 2 % mercury cyanide or $2\text{ }^{\circ}/_{00}$ mercury chloride or 1.2 % saponin, all dissolved in 0.9 % NaCl solution. After mixing the glasses are stoppered and placed in a thermostat of 37° for 2 hours. Then the glasses are shaken so much that the precipitate is whirled up; if there is agglutination, the faintest degree of it will present itself as small distinct flakes (recorded as +), a stronger degree presenting itself as larger flakes or threads which are more or less coalescent, forming a larger, loose lump or network (recorded as ++), and the strongest degree appearing as a coherent membrane covering the bottom of the glass and, in the course of a couple of minutes, re-

tracting more or less into a ball the size of a hampseed (recorded as +++). The agglutination is so strong that it does not dissolve, even if the glass is shaken fairly vigorously. Microscopy discloses that the coagulum consists of closely packed blood platelets and many leukocytes, no fibrin threads being seen, however; in the surrounding plasma are still found many free or slightly agglutinated blood plates. As to saponin the conditions are a little different, for, if ordinary citrate plasma is added to it, the blood platelets will be dissolved, but if the blood is heated to 42° , some of the blood plates will undergo a change and agglutinate on addition of saponin, whereas the rest is dissolved; on the other hand, if the saponin concentration is weaker, only agglutination will ensue. The microscopical picture resembles that found by the mercury salts, but the plates fuse more and are badly outlined, and in the surrounding plasma, only isolated shadows of blood plates are seen.

On examining a number of normal individuals, the agglutination was found to be of rather different strength, a few of them presenting fairly weak agglutination with the afore-named concentrations, others very strong agglutination.

In order to obtain a quantitative measure for the agglutination of the plates it was endeavoured to find out the smallest quantity of the substance required for causing a faint, macroscopically visible agglutination. For mercury cyanide the concentration in the samples varied between $2^{\circ}/_{00}$ and $0.125^{\circ}/_{00}$, for sublimate between $0.18^{\circ}/_{00}$ and $0.08^{\circ}/_{00}$, and for saponin, between $1.5^{\circ}/_{00}$ and $0.8^{\circ}/_{00}$. Sublimate in the weakest concentrations, however, giving the sharpest limit, this substance was selected for a closer examination of the agglutination in normal and some pathological conditions. The experiments being performed with the same blood sample, the reactions were rather uniform for the three substances, though somewhat weaker on applying mercury cyanide. The procedure in all the experiments was as follows:

Technic: 20 cm^3 of citrate blood (as a rule, however, 10 cm^3 will suffice but in isolated cases with a very low S. R., 30 cm^3 will be required) are placed on a thermal water bath of 42° for 3 hours, after which all the supernatant plasma is pipetted off. After careful mixing of this plasma, 10 small test-tubes are charged with 0.5 cm^3 of it each. To each tube is added 0.05 cm^3 of a number of solutions of

mercury chloride (this is easiest with the help of a micropipette a. m. Levy). The mercury solution contains from 0.7‰ to 1.6‰ of mercury chloride dissolved in 0.9‰ of NaCl solution and with a difference of 0.1‰ so that the concentration in plasma becomes 0.07‰ — 0.08‰ — 0.09‰ 0.16‰ . After shaking the glasses are stoppered and placed in a thermostat of 37° for 2 hours. Then the tubes are shaken so that the precipitate whirls up, and readings are made after the above-named nomenclature. In the following, the tubes presenting agglutination will be marked 7, 8, 9, etc. corresponding to concentrations of mercury chloride of 0.07‰ — 0.08‰ — 0.09‰ etc.

With a view to the influence of temperature on the strength of the agglutination, experiments were performed at 45° — 42° — 40° — 37° . The reactions obtained at 45° and 42° are identical, however, the agglutination obtained at 40° being somewhat weaker, and no agglutination being found at 37° .

As regards the importance of the reaction time, some agglutination was found in the blood samples already after 1 hour's standing at 42° , strong agglutination after 2—3 hours, the strongest agglutination, however, as a rule being found after 3 hours, this time was selected in all the experiments. After 5 hours' standing, the reaction will be much weaker, which must probably be attributed to the circumstance that the blood platelets with the greatest agglutinability have sunk down, for after that lapse of time the number of blood plates will decrease by about 10 per cent, as was shown before.

This can be substantiated by all the citrate plasma after 3 hours' standing being pipetted off (under sterile precautions) into another tube which is then again allowed to stand at 42° . Now, on determining the agglutinability every third hour after vigorous shaking of the tube, it will be seen that, the longer the blood plates are exposed to the action of heat, the weaker a concentration of sublimate will be required for agglutination. After the lapse of 10—12 hours, agglutination will appear without addition of sublimate. Fig. 1 illustrates such an experiment, the curve showing the smallest quantity of sublimate required just to produce agglutination after standing, partly at 42° , partly at 40° . The reaction recorded at 40° is much lower than at 42° , and whereas spontaneous agglutination appears after 12 hours at 42° , it does not appear before 26

hours have elapsed at 40°. The time elapsing before spontaneous agglutination appears at 42° in normal individuals, varies between 8 and 15 hours, parallelling the strength of reaction determined after 3 hours with the above procedure.

If heparin in a concentration of from 5 to 20 mg % is added to the plasma before the addition of sublimate, mercury cyanide and saponin, the agglutination can be inhibited. I shall revert to this later.

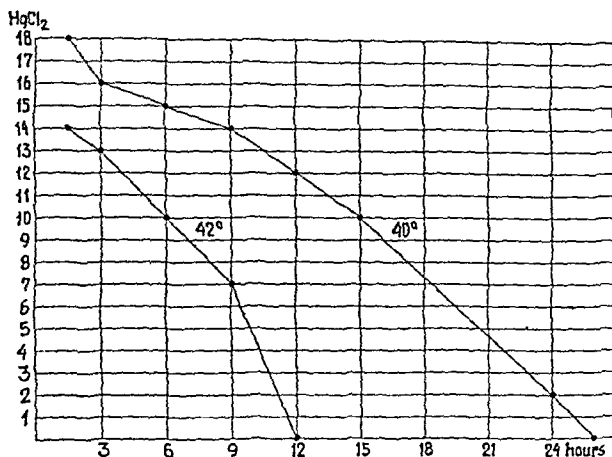


Fig. 1.

What happens with the blood platelets when the blood is allowed to stand at 42°, whether there is a question of a change in the milieu or in the blood plates themselves, cannot be explained yet. Thus a P_H deviation towards the acid side, by which the negatively charged platelets agglutinate more easily, apparently is not the cause, for on measuring the P_H in plasma which had been standing for 3 hours at 37° and 42°, respectively, it was found to be the same or but little lower at 42°. A discharge of the platelets by addition of the salts employed, such as Starlinger & Sametnik have found for lanthanum nitrate, is out of the question, for mercury cyanide practically is not dissociated, mercury chloride being but slightly dissociated, and saponin not at all.

Lysolecithin prepared a. m. Singer had no effect on the agglutination of the blood platelets.

There is no question of a profibrin formation, i. e. the soluble prephase of fibrin (Apitz), for neither in a suspension of kaolin in

plasma free from platelets which had been treated with heat, nor in a suspension of red blood cells was any agglutination found after addition of sublimate.

In order to find out whether the change involves blood platelets or plasma, two samples of citrate blood from the same patient were placed at 18° and 42°, respectively, for 3 hours, and the platelets in the supernatant plasma were then centrifuged down. When the blood platelets had been washed once in a physiol. NaCl solution, the thermally treated blood plates were suspended in the non-thermally treated plasma free from platelets, and vice versa. After addition of 2 0/100 sublimate in the proportion of 1: 10 to both samples, which were then placed at 37° for 2 hours, pronounced agglutination was found in the tube containing thermally treated blood platelets in ordinary plasma but not in the other sample. On the other hand, a suspension of thermally treated blood plates in physiological saline, gave no agglutination. These experiments indicate that an action anyhow is exerted on the blood platelets themselves but that the agglutinations only can take place in plasma. In the same direction points the fact that plasma which has been standing at 42° for 24 hours, after removal of the platelets by centrifugation does not enhance the agglutination when it is added to the plasma which has been treated with heat in the ordinary manner. Probably there is a question of an action on the adsorbing surface membrane of the platelets, certainly a degenerative change due to denaturation of the protein substances, which renders the platelets viscid. As was mentioned before, a thermal action of longer duration alone is able to give rise to this change, but the process is accelerated by Hg. salts and saponin which, alone, are not able to bring about a corresponding denaturation process, however. Moreover, it seems as though only a certain percentage of the blood plates were influenced and could be caused to agglutinate, for even if the concentration of the three substances is added in increasing quantities, they are only in a certain maximal degree able to cause agglutination of platelets.

As was previously mentioned, the agglutinate contains several leukocytes too, but, as yet, it is impossible to say how great a part they play.

It is peculiar and interesting that the same three substances which give rise to agglutination, influence the membrane of the red

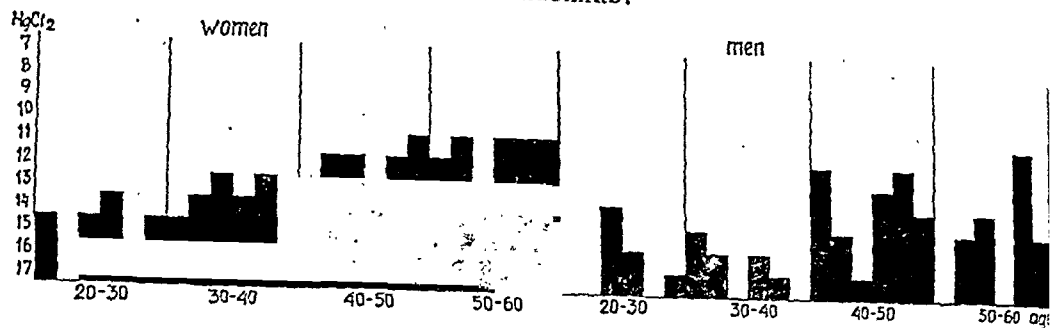


Fig. 2.

blood corpuscles also. Saponin and sublimate give rise to hemolysis, and mercury cyanide even in very small concentrations according to Bjerring influences the membrane of the red blood corpuscles so that they become impermeable for glucose but remain permeable for urea, and it shall be mentioned that the substance has a strongly inhibiting action on the sedimentation of the blood.

On applying the mentioned method with sublimate, determinations of the agglutination of the blood platelets were performed partly on blood from normal individuals and partly under pathological conditions, which will be discussed in the following; finally will be recorded some experiments carried out in order to study the heparin influence.

Normal Individuals.

As normal individuals were considered patients suffering from slight affections without fever and with a normal sedimentation rate, chiefly patients with myoses, slight disturbances of the intestinal canal, neurasthenia etc.

Altogether 24 men and 24 women aged from 20 to 60 years were examined. In Fig. 2 are recorded the results arranged according to sex and age, each column thus representing one patient and the number of tubes in which agglutination was found. From the Figure it is evident that there are some individual differences, and that the agglutinability increases with advancing age, notably in women, in whom it is on the whole much higher than in men; thus there was found only a single quite negative reaction in women, whereas there were found seven in men.

It is thus impossible to indicate quite exact a normal value, regard must be paid to both sex and age, and all that can be said is that plasma which agglutinates more than in glass 10, must be regarded as pathological in patients aged less than 60 years.

If several determinations are made on the same individual at days' intervals, the same results are obtained or merely a deviation of \pm in one tube; in some patients, however, for example several patients with *ulcus ventriculi*, a decrease of the values was found during their hospital stay. Of the importance of this nothing can be said at present.

Febrile Affections.

On 10 patients with different acute febrile affections were performed repeated determinations of the agglutination of the blood platelets. In all the patients the agglutinability of the plates was found to be distinctly increased, and the degree of this increase seemed partly to depend of the gravity of the infection, and partly of the patients' ages, older persons presenting a greater increase than younger ones. The proportion between temperature, S. R. and agglutination of the blood platelets (expressed by the tube with the weakest concentration of Hg Cl_2 still giving agglutination) in a male patient with bilateral pneumonia, is recorded in Fig. 3. From the Fig. it is evident that the agglutination of the blood platelets is increased but that the maximum of agglutinability is not reached till some time after the onset of the disease when the temperature decreases, subsequently persisting high for a long time, and not till the temperature has been normal for a fortnight, does a decrease take place, whereas the S. R. decreases immediately after the termination of the febrile period. This applies to all the ten patients whose data are recorded in Table 1, where both the maximal increase of the agglutination and the highest S. R. found are noted but, as was mentioned before, they do not always coincide

Moreover, two patients with more protracted infections, namely, pulmonary abscess and miliary tuberculosis, are mentioned. The highest rise that was found in these 12 patients is that represented by tube 7, being found in 4 patients. Nor were any higher values found in the entire material of patients, not even in those with thrombophlebitis, as will be shown later.

Table 1.

Age	Sex	Disease	S.R.	Tubes with Hg Cl ₂								
				15	14	13	12	11	10	9	8	7
19	♀	Pneumonia duplex	115	+++	+++	+++	+++	+++	+++	++		
22	♂	»	108	+++	+++	+++	+++	++	+			
46	♂	»	106	+++	+++	+++	+++	+++	+++	+++	++	+
32	♀	» Absces. abdom.	120	+++	+++	+++	+++	+++	++	+		
38	♀	Morbus Weillii	82	+++	+++	+++	+++	+++	+++	+++	++	+
40	♀	Bronchopneumonia	59	+++	+++	+++	+++	+++	++	+		
40	♀	Febris rheumatica	80	+++	+++	+++	+++	+++	++	+		
46	♂	Erythema multiforme	63	+++	+++	+++	+++	+++	++	+		
42	♂	Absces pulm.	117	+++	+++	+++	+++	+++	+++	+++	++	+
45	♂	Tub. miliaris	16	+++	+++	+++	+++	+++	+++	++	++	+

Affections with Normal Temperature but with Increased Sedimentation Rate.

In order to find out whether the humoral changes causing an increase of the S. R., influence the agglutination of the blood platelets too, this latter was determined in a number of patients with affections giving rise to increased S. R. but in whom the temperature was normal.

A tendency to increased agglutination of the erythrocytes being due to discharge of their electric charge particularly on account of an increase of globulin and fibrinogen, it must be anticipated that the same changes would influence the electric charge of the blood platelets in the same direction and, thus, increase the tendency to agglutination. In Table 2 are recorded determinations of the agglutination of the platelets of 15 patients with greater or minor sedimentation reaction, arranged after its strength.

Table 2.

Age	Sex	Disease	S.R.	Tubes with Hg Cl ₂								
				15	14	13	12	11	10	9	8	7
19	♀	Gravid. mens VII	28	+++	+++	+++	+++	+++	+			
56	♀	Haemorrhagia cerebri	30	+++	+++	+++	+++	++	+			
24	♀	Tub. pulm. Gravid. mens VII	36	+++	+++	+++	+++	+++	+++	++	+	
57	♂	Cancer ventriculi	40	+++	+++	+++	++	+				
48	♂	Cancer hepatis	42	+++	+++	+++	+++	+++	+++	+		
45	♀	C. mammae c. metast.	50	+++	+++	+++	+++	+++	+			
48	♀	Nephrosclerosis	55	++	++	++	++	++	++			
23	♀	Gravid. mens V	58	+++	+++	++	+	+				
54	♀	Polyarthroitis chr.	64	+++	+++	+++	+++	+++	++			
25	♂	Polyarthroitis chr.	80	+++	+++	+++	++	++	++			
44	♂	Polyarthroitis chr.	108	+++	+++	+++	+++	+++	+++	+		
44	♀	C. uteri c. metastase	112	+++	+++	+++	+++	+++	+++	+++	+++	+
57	♂	Tumor pulm.	120	+++	+++	+++	+++	++	++			
43	♂	Hypernephroma	130	+++	+++	++	++	+				
41	♂	Lymfogr. granulomatose	132	+++	+++	+++	++	+	+			

Here it will be seen that there was a pronounced increase of the agglutination of the platelets in nearly all the cases, but in one single case only was a very strong reaction to tube 7 found, whereas reaction to tube 11 was found in 4 cases. There is no parallelism between the agglutination and the S. R., it can only be said that in patients with increased S. R., the agglutinability of the blood platelets is increased more or less considerably; regard being paid to the patient's age, a particularly low agglutination of the platelets was not found in any patients with distinctly increased S. R.

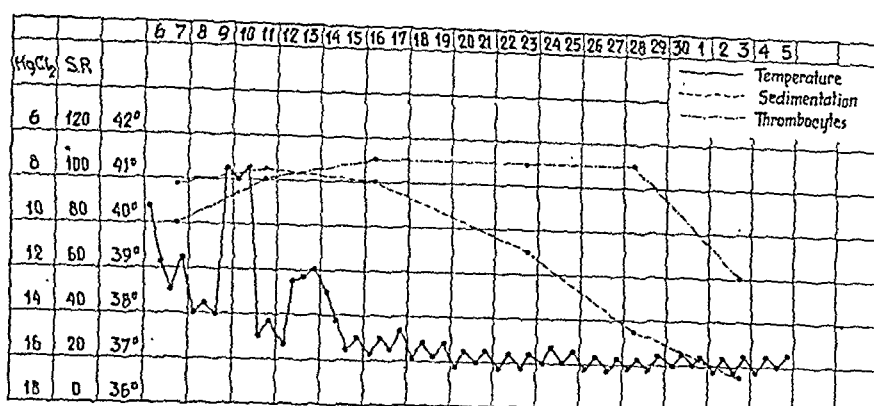


Fig. 3. The agglutination of the blood platelets in a 46 year old man with pneumonia duplex (treatment: 40 gm. of lucosi).

Operation Patients.

On account of the wellknown disposition to thrombosis after surgical operations, it would be of interest to examine the agglutination of the platelets in a number of operated patients¹. The material only comprises 7 patients, 5 women and 2 men, 6 of whom had been submitted to laparotomy, but the detected changes were rather plain. Fig. 4 shows the result, the agglutination of the plates being recorded in the same manner as on Fig. 3. It will be seen that a distinctly increased agglutination occurred in all the cases, a distinct increase occurring already after 2—3 days and reaching its maximum on the 5th to 8th day, subsequently decreasing more or less slowly. The highest increase was found in a 54 year old woman who incurred a lung infarct 8 days after the operation.

Thrombophlebitis and Lung Infarct.

As was mentioned introductorily, it must on the ground of our present conception of the pathogenesis of thrombosis be anticipated that the agglutination of the blood platelets would be found to be greatly increased in patients with these affections.

¹ I am indebted to the director of the surgical department of the Copenhagen County Hospital, Chief Physician H. Wulff, for permission to draw blood samples from patients who were under his care.

Table 3.

Age	Sex	Disease	Tubes with Hg Cl ₂								
			15	14	13	12	11	10	9	8	7
26	♀	Phlebitis ext. inf. Pleuritis exsud.	+++	+++	+++	+++	+++	+++	+++	+	+
46	♀	" " "	+++	+++	+++	+++	+++	+++	+++	++	(+)
52	♀	" " " Polyarthrosis chr.	+++	+++	+++	+++	+++	+++	+++	++	+
53	♀	" " Mb. cordis	+++	+++	+++	+++	+++	+++	+++	+++	++
56	♀	" " Mb. cordis	+++	+++	+++	+++	+++	+++	+++	+++	++
56	♀	" "	+++	+++	+++	+++	+++	+++	+++	++	+
62	♂	" " Thrombosis a. coron. seq.	+++	+++	+++	+++	+++	+++	+++	++	+
64	♀	" " Arthrosis genuum	+++	+++	+++	+++	+++	+++	+++	++	+
28	♀	Infarkt. pulm. post operat.	+++	+++	+++	+++	++	+			
48	♀	" " " "	+++	+++	+++	+++	+++	+++	++		
54	♀	" " " "	+++	+++	+++	+++	+++	+++	++	+	

Eight patients with thrombophlebitis and 3 patients with lung infarct after operation were examined. The results are recorded in Table 3. In all the 8 thrombophlebitis patients was found very strong agglutinability, namely, to tube 7, and the same applies to one patient with lung infarct, a less strong reaction being found in another younger woman with a slighter infarct.

From the first days the reaction is maximal and, according to the gravity of the case, remains high for other 8—14 days, subsequently decreasing rather slowly.

The Effect of Heparin.

Best & Cowan & MacLean have shown that heparin besides influencing the coagulation of the blood also exerts an inhibiting action on the agglutination of the blood platelets. As was mentioned

before, heparin on being added to the thermally treated plasma is able to check the agglutinating action of sublimate, mercury cyanide, and saponin.

On examining the smallest quantity of heparin which is able to check the agglutination, it will be found that it depends of the strength of the agglutination; in plasma with weak agglutination, a concentration of 2—5 mg % only is required, whereas 20—30 mg % are required in plasma with strong agglutination.

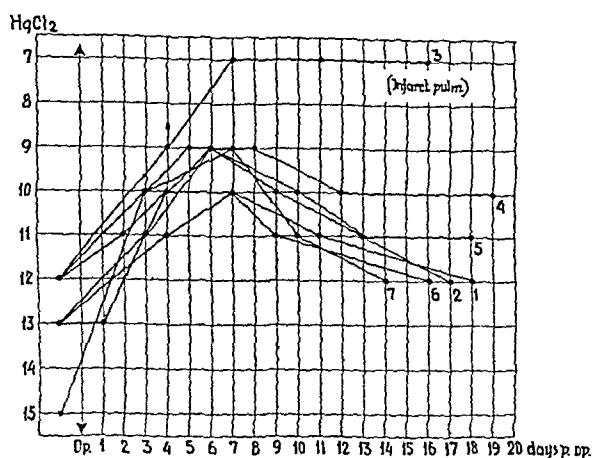


Fig. 4. 1. ♀ 44 years Ovariectomy. 5. ♂ 30 years Resectio ventriculi.
2. ♀ 26 years Amp. uterisupravag. 6. ♀ 49 years Kolporrhaphia ant.
3. ♀ 54 years Cholecystectomy. 7. ♂ 56 years Appendectomy.
4. ♀ 46 years Cholecystectomy.

This determination of the smallest quantity of heparin which can prevent agglutination, is somewhat difficult, however, for plasma to which is added heparin plus one of the afore-named three substances, after 2 hours standing at 37° becomes somewhat viscid so that the tubes must be shaken rather vigorously in order to check the existing tendency to agglutination in contradistinction to the otherwise very firm agglutination. This applies particularly to sublimate and saponin, in a minor degree to mercury cyanide.

If heparin is added to the blood before it is placed at 42° for sedimentation, the result is the same, but in this case a weaker concentration of heparin is required for checking the agglutination, and here, too, the plasma becomes somewhat viscid after addition of heparin plus sublimate.

In order to ascertain the dependency of the agglutination on the addition of heparin in this procedure, heparin in increasing concentrations was added to a number of tubes with citrate blood from the same patient, the weakest concentration of sublimate causing agglutination afterwards being determined in the usual manner. From Fig. 5, where the dependency of the agglutination on the heparin concentration is recorded, it is evident that the inhibition is but slight in weak concentrations, but that it is followed by a strong effect. This corresponds to the extension of the coagulation time through addition of heparin.

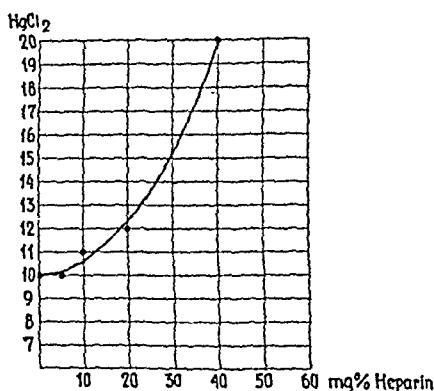


Fig. 5. The dependency of the agglutination of the blood platelets on the heparin concentration.

In patients with great agglutinability of the blood platelets, the ascending part of the curve on Fig. 5 will be displaced towards the right and, inversely, towards the left in individuals whose blood platelets have but little tendency to agglutination.

As regards the question whether heparin exerts the same action on blood platelets *in vivo*, 5 patients were submitted to injections of various quantities of heparin, and blood samples were drawn after 15 and 60 minutes for determination of the agglutination. From Table 4 it is evident that an effect is not obtained before 250 mg of heparin or more have been injected, and that the effect even of 400 mg is neither particularly strong nor of long duration, having decreased distinctly after the lapse of 1 hour.

This agrees with the results of experiments with dogs performed by Solandt & Best who found that small doses of heparin had no effect on the agglutination of the blood platelets, the agglutina-

Table 4.

Disease	Inj. of Heparin	Tubes with Hg Cl ₂									
		Time	15	14	13	12	11	10	9	8	7
Thrombosis a. coronar	150 mg	Before inject.	+++	+++	+++	+++	++	++	+		
		15 min.	+++	+++	+++	+++	+++	++	+		
		60 min.	+++	+++	+++	+++	+++	++	+		
Emollitio cerebri	175 mg	Before inject.	+++	+++	++	++					
		15 min.	+++	+++	++	+					
		60 min.	+++	+++	++	++					
Cancer ventriculi	250 mg	Before inject.	+++	+++	++	+	+				
		15 min.	+++	++	+						
		60 min.	+++	++	++	+					
Hæmorrhagia cerebri	400 mg	Before inject.	+++	+++	+++	++	+				
		15 min.	+++	++							
		60 min.	+++	+++	+						
Lymfogramulomatosis	400 mg	Before inject.	+++	+++	+++	++	++	+			
		15 min.	++	++	+	++					
		60 min.	+++	+++	+++	++	+				

tion of the plates not being inhibited till larger doses of 3 mg per kg body weight had been applied, but the effect was of shorter duration than the effect on the coagulation.

How is this effect of heparin to be explained? The system contains neither thrombokinase nor thrombin with which heparin can

combine. However, if what happens when the plasma is allowed to stand at 42° is regarded as an incipient denaturalization of the protein substances, Fischer has shown that, if a system containing genuine homogenous protein substances plus heparin, is exposed to thermal action, the latter will protect the protein substances against coagulation, because it will block up the basic components formed thereby.

Besides heparin, citrate plasma which has not been exposed to thermal action, likewise has an inhibitory effect on the reaction. Thus, on adding 0.1 or 0.2 cm³ of unheated plasma without blood platelets from young normal individuals, to 0.5 cm³ of thermally treated plasma before sublimate is added to it, a faint though distinct inhibition of the agglutination is obtained (from 1 to 3 tubes). On the other hand, on using unheated plasma without blood platelets derived from patients who have presented very strong agglutination of the platelets, no inhibition of the reaction is obtained.

Discussion.

Already Aschoff has shown that the formation of an intravital thrombus is quite different from the coagulation observed in test tube experiments, the very inception of thrombosis being an agglutination of blood plates without synchronous formation of fibrin. The fibrin appears secondarily, the primary phenomenon in thrombus formation is not a coagulation but an agglutination of platelets. The factor giving rise to this platelet agglutination has been thought to be a lesion of the intima of the vessel (Dietrich, Ritter and others), such a lesion not always being detectable, however, liberated thrombin has nevertheless in recent years been made responsible for the agglutination (Apitz, Lenggenhagen, Wöhlisch and others). If synchronous fibrin formation is not detectable, it is, according to Apitz, due to the formation of a soluble prephase of fibrin, i. e. profibrin or, after Lenggenhagen, to the freshly sedimented fibrin immediately being adsorbed to the surface of the blood platelets and, hence, not visible on application of the usual methods of fibrin demonstration. According to these hypotheses, agglutination of blood platelets and subsequent thrombosis formation should thus not be possible without synchronous existence of thrombin.

However, as was shown in these investigations, a fairly strong agglutination of the blood plates may be obtained in plasma from which Ca^{++} was removed and which, consequently, cannot be assumed to contain thrombin, by allowing the plasma to stand at $40-42^\circ$ for from 10 to 24 hours, i. e. under conditions which may be thought to occur in the organism under pathological conditions; moreover, that certain hemolytic active substances are able to promote this agglutination.

The question therefore must be whether the same process may be thought to take place *in vivo*. A stagnation of the blood at $40-42^\circ$ is conceivable in highly febrile conditions, possibly with synchronous formation of toxic substances whose effect was analogous to saponin, sublimate, and mercury cyanide, that means to say, with an accelerating effect on the platelet agglutination. On the other hand, however, do thromboses occur far more frequently in patients whose temperature is not increased and in whom there cannot thus be a question of any thermal action on the blood platelets. It must therefore be assumed that there is a question of the formation of another noxa with analogous effect which influences the blood plates which are less stable than in other patients.

Even though the pathogenesis of platelet agglutination *in vivo* is not quite identical with the conditions under which it is caused in these *in vitro* experiments, the question whether the results derived from the method applied, does not afford an expression of the minor or greater tendency to agglutination *in vivo* of the blood platelets.

Several facts might, perhaps, be suggestive of this. On examining a greater number of thrombosis cases occurred after operations, Dahl-Iversen & Ramberg found that this complication was far more frequent at the ages of between 40 and 65 years, and corresponding conditions were found by Linde. Among the total number of cases, $\frac{2}{3}$ were found in women, and $\frac{1}{3}$ in men. On examining the agglutination of blood platelets in normal individuals, it was correspondingly found to increase with advancing age, and that, on the whole, it was stronger in women than in men.

The same conditions which are the most frequently associated with thrombophlebitis and infarcts after operations (particularly laparotomy), severe infections, and in debile patients with severe chronic affections, were found to present a distinct increase of the

agglutinability of the platelets. In the operation patients who were submitted to examination, the reaction was found to be strongest from the 4th to 8th day after operation, corresponding to the space of time when the cases of thrombosis were of most frequent occurrence in Dahl-Iversen & Ramberg's material of patients. Moreover, 8 patients with thrombophlebitis presented the strongest reactions.

Corresponding to the effect of heparin as a prophylactic remedy against thrombotic conditions, it was found that it has an inhibiting action on the reaction employed for determining the agglutination of the platelets both *in vitro* and after injection on patients.

As is evident from the experimental results, strong agglutinability was found in several patients with febrile affections, and in a few patients with more chronic affections, without any signs of phlebitis or infarct being found; however, as was mentioned before, it must be assumed that, besides an agglutination of the platelets, other factors play a part, too, before a thrombus can form, particularly a decreased blood perfusion. Possibly, it frequently comes to formation of small blood thrombi in such patients though, on account of a good circulation, without becoming the starting-point of a thrombus.

An eventual explanation of the blood plate agglutination thus does not solve the entire phlebitis question, but a determination of the agglutinability of the plates may possibly afford information with regard to the patients's greater or minor disposition to thrombus formation, and thus give a hint with regard to an eventual prophylactic treatment.

To substantiate this, however, is required partly a greater material of patients, especially operation patients, than the present, partly an investigation in the question whether patients who have previously had phlebitis, preferably are found among those individuals whose blood platelets present great agglutinability.

Summary.

1. If citrate blood for sedimentation is placed at 42° for 3 hours, the addition of small quantities of mercury cyanide, mercury chloride or saponin to the blood platelet-containing plasma, gives

rise to so strong an agglutination of blood plates that it is macroscopically perceptible. The reaction does not appear at a temperature below 40° .

2. A corresponding agglutination of the blood platelets appears in platelet-containing citrate plasma which is allowed to stand for about 12 or 24 hours at 42° and 40° , respectively, without addition of the above-named substances.

3. It seems as though only a certain percentage of the blood platelets can be caused to agglutinate, and this agglutination seems to be due to an action on the very blood plates, probably an incipient denaturation of their surface membrane.

4. The author has elaborated a quantitative method for determining the agglutinability of the blood platelets, the smallest quantity of sublimate being determined which gives rise to a macroscopical agglutination in blood platelet-containing plasma which has stood in a temperature of 42° for 3 hours.

5. In 48 normal individuals aged from 20 to 60 years, the agglutinability of the platelets was found to be fairly oscillating, being weaker in men than in women, and increasing distinctly with advancing age notably in the latter.

6. In patients with acute febrile affections, a considerable increase of the agglutination occurs particularly at a somewhat advanced stage of the illness, followed by a slow decrease of the reaction.

7. In patients with afebrile affections associated with a greater or minor increase of the agglutinability is found, but there is no parallelism between it and the S. R.

8. In 7 operation patients was found a distinct increase of the agglutinability already after the 2nd to 3rd day, with a maximum on the 6th to 8th day, followed by a slow decrease.

9. In patients with thrombophlebitis and lung infarct was found strong agglutination of the blood platelets.

10. On addition of heparin either to citrate blood before it being placed at 42° , or to the thermally treated plasma, the agglutinating effect of mercury cyanide, mercury chloride and saponin is checked. If heparin is injected, the agglutination is likewise inhibited though only for a fairly short time, considerably greater quantities being required than those necessary for affecting the coagulation. Non-heated plasma from normal individuals has an

inhibiting effect too, whereas plasma from patients whose blood platelets have shown very strong agglutination, does not exert such an inhibiting action.

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Epidemic hepatitis in the county of Västerbotten in Northern Sweden II.

Continued epidemiological and clinical studies.

By

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(Submitted for publication June 17, 1943).

In a study published last year as supplementum CXL to the *Acta Medica Scandinavica* the author surveyed different epidemics of hepatitis occurring in the county of Västerbotten in the years 1937—1942 from the epidemiological point of view. In addition, so far as available clinical data permitted an analysis some aspects of the nosography were gone into. The experience obtained in the course of that investigation indicated that on account of our insufficient knowledge of inter alia, the spread of the disease, a rare opportunity was missed to enhance our knowledge concerning what was going on in the body prior to the onset of illness, especially with regard to the distribution of bile pigments.

Owing to propitious circumstances in the shape of another institutional outbreak, the author now has been able to make a contribution on this subject. The evidence of this last outbreak incidentally provides a welcome check on the epidemiological conclusions reached in the earlier study. In addition, this present investigation has brought to light certain facts regarding the occurrence during an epidemic of an appreciable number of slight liver

Epidemiology. As an introduction, and, by the way of a post script to my earlier study, it may fittingly be reported that no fresh cases of hepatitis have occurred among the consumers in Vännäs, since steps were taken to purify the water supply. Accordingly the assumption that the Vännäs epidemic was waterborne gains further credence.

The two distinct but presumably interrelated epidemics now to be described show different characteristics.

The *Bjurholm* cases were scattered among the different centres of settlement along the road between Bjurholm and W. Örträsk. The *Nordmaling* outbreak occurred in *Strömsör*, an asylum for the feeble minded, situated 10 kilometres north of Nordmaling. There is no direct road connection between the Bjurholm area and the asylum, and no demonstrable intercourse. The Öre river, however, serving on the one hand as recipient to the Bjurholm area and on the other as the source of water supply to the asylum forms a relevant connecting link.

Bjurholm. Referring to my general survey of the prevalence of hepatitis, it will be found that the Bjurholm district was practically spared visitation by the disease during the years when the adjoining districts Vännäs and Vindeln were the scenes of extensive epidemics.

To judge by the monthly reports the disease appears to have gained a foothold in the latter half of 1942, the returns being:

1942								1943.	
July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Febr.	March	April
2	3	1	4	7	5	7	12	2	9

Later investigation has revealed a considerably greater morbidity which could, of course, be expected. It has not been possible to find out how the infection was introduced into the district. The first person who was taken ill on Oct. 7th was living in *Provåker*, a small village of 92 inhabitants, comprising a dozen families each living in a house of its own. Subsequently, cases occurred at varying intervals among the neighbours, several members of the different households falling ill at about the same time. Thus 3 persons in one family were taken ill on Nov. 11th, 3 members of another family between Dec. 5th and Dec. 12th and 2 additional cases in separate houses on Dec. 5th and Jan. 21st respectively. From *Provåker* the

disease spread to adjoining villages on both sides. In *Sunnaná*, with 143 inhabitants, 3 members of a family came down with the disease during the time Jan. 3rd—Jan. 20th. At about the same time, or on Jan. 9th, to be exact the first case was reported from *Örebro*, a small settlement numbering 29 persons, and situated upstream from *Provåker*. Forty days later 6 members of the same family were taken ill, suggesting simultaneous infection either by contact or aborally.

Finally 2 family outbreaks were observed in *Öreström* (120 inhabitants) in as much as husband and wife in one house were taken ill on March 16th, and in another between April 7th and 10th.

The Bjurholm cases do not permit of any conclusions regarding the mode of infection. Opportunities for contact between individuals from the different small villages have not been lacking. In particular, during the Christmas festivities a lively intercourse has taken place, providing possibilities for a transfer of the disease in different ways. River water apparently has not been used in any of the afflicted households. Wells and sanitation are of the usual rural type. The characteristic accumulation of coincident cases in the same families recalls the experiences from other hepatitis epidemics at home and abroad where a waterborne contagion has been suspected. Whatever the mechanism of infection, a point to be kept in mind is that the Öre river, being the recipient of the waste products from the whole visited area, unavoidably became infected.

Nordmaling.

In the third week of January 1943 three cases of hepatitis were notified by the district medical officer in Nordmaling, all of them having occurred among the inmates of the asylum for the feeble minded at Strömsör, situated on the left bank of the Öre river near its mouth. This institution which has an aggregate population of patients and personell numbering 150 persons is fairly effectively isolated. Most of the patients have been in the asylum for many years and admittances as well as discharges are infrequent, visitors few.

Experience has taught us that institutional epidemics, on account of the simplified conditions they present, are liable to throw valuable side lights on the epidemiological, as well as the clinical aspects of a contagious disease. The Hällnäs epidemic of

bidity of 22.7 ± 3.4 %. In the Hällnäs outbreak a case incidence of 34.4 ± 3.5 % was reported. The difference, 9.7 ± 4.98 %, is not statistically proven. Considering the accumulative concentration of the contagion in the Hällnäs epidemic as against its gradual dilution in the Öre river one would have expected an appreciably lower morbidity in the Strömsör outbreak.

Table 1.

Number of hepatitis cases = N on different dates in the Sörfors outbreak.

Date	N	Date	N	Date	N
Jan. 13	1	Jan. 31	1	Febr. 18	
14		Febr. 1		19	1
15	1	2		20	1
16		3		21	
17		4		22	
18	1	5	2	23	
19	1	6	1	24	1
20	1	7	1	25	2
21		8		26	
22	3	9		27	
23	2	10	2	28	
24		11	1	March 1	
25		12		2	
26	1	13	3	3	
27	1	14		4	1
28	1	15		5	
29	1	16	1	6	1
30		17	1	7	

The age distribution reveals the same relative immunity in the third and later decades of life, no hepatitis patient being over thirty. The morbidity fluctuates between 53.85 ± 13.05 % and 24.00 ± 8.54 % in the 5—9 and 25—29 year groups respectively. difference 29.85 ± 15.6 % is not statistically significant or probable; but the figures are too small to admit of conclusions. See table 2.

In order to settle the old controversy whether or not hepatitis is preeminently a children's disease it is, as the author has explained in this thesis, necessary to know not only the age distribution among those who are taken ill but also that of the exposed

population. This can only be assured in closed institutions where stable demographic conditions reign. The opportunities to encounter the necessary propitious combination of mass infection and a properly tabulated exposed population are extremely rare. This

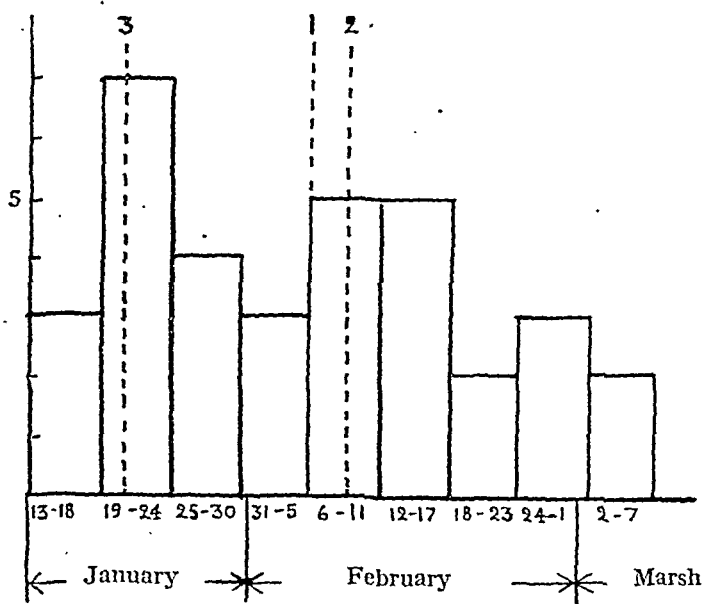


Fig. 2.

Number of cases of hepatitis in the Strömsör population

1 = Median = Febr. 5—6th

2 = Mean = " 8th

3 = Water boiled from Jan. 20th.

being the case and considering the striking similarity in many respects between the Hällnäs and Strömsör outbreaks, not least regarding the conformable morbidity, it appears permissible to combine the two materials in order to obtain figures of a magnitude to enable us to form an opinion. See table 3.

From the collocation it may be gathered that children in the first lustre of life are less liable to contract the disease than older children or adults. Between 5 and 25 years we find no significant differences of morbidity between the different 5 years' periods. After 25 years of age the liability to catch the disease gradually decreases and no person in the material above 45 is known to have been taken ill.

Accordingly it can be maintained that epidemic hepatitis does not show any preference for school age or adolescence.

Table 2.

Age distribution in the Sörfors population and frequency of hepatitis in the different age groups. $P \pm \epsilon$ (P) percent of the population ($= N$) \pm standard error of the percentage.

Age in years	N	Hepatitis cases	$P + \epsilon$ (P)
0--4	2		
5--9	13	7	53.85 ± 13.05
10--14	20	6	30.00 ± 9.49
15--19	21	7	33.33 ± 10.29
20--24	20	8	40.00 ± 10.95
25--29	25	6	24.00 ± 8.54
30--34	11		
35--39	18		
40--44	9		
45--49	4		
50--54	5		
55--59	1		
60--64			
unknown	1		
	150	34	22.66 ± 3.42

Clinic.

Banking on the possibility of an accumulation of hepatitis cases in the Strömsör asylum the author decided to pry into the secrets of the incubation stage, especially regarding the distribution of bile pigments as an indication of damage to the liver. By examining blood tests taken at regular intervals from the whole population one would expect to obtain series of observations on serum-bilirubin concentrations prior to the onset of illness and thus be able to form an idea of when the liver becomes involved, which assuredly has a bearing on the problem of infectiousness.

Method.

It would have been desirable to employ the citric acid and phosphatase tests for this investigation but the equipment at the authors disposal made this impossible. The choice had to be made between the Meulengracht and the Hijman van den Bergh's tests

both of which had been used earlier by the author when determining the duration of the icteric stage. Experience gained during that investigation seemed to indicate close agreement between the two methods. The Meulengracht test is by far the more expeditious and its variations in normal persons have been established. Preference was, however, given to the Hijman van den Bergh's test on account of its claim to enable conclusions to be drawn about the anatomical site of the liver lesion by comparing the results arrived at by the direct and indirect methods. The choice necessitated an investigation in order to determine the limits of the readings in healthy persons. To this end a sufficient number of conscripted soldiers and hospital employees was tested

The Hijman van den Bergh's test in healthy subjects.

99 persons were examined. The mean of these readings was found to be $= 0.49 \pm 0.02$, the median $= 0.5$ and the standard deviation

Table 3.

Age distribution in the combined material from Hällnäs and Strömsör and frequencies of the disease in different age-groups.

N = number of exposed individuals. n = number of hepatitis cases.

$P \pm \epsilon (P)$ percentage of cases and standard error of percentage.

Age in years	N	Hepatitis cases = n	$P \pm \epsilon (P)$
0—4	21	2	9.52 ± 6.40
5—9	35	13	37.14 ± 8.17
10—14	61	23	37.70 ± 6.21
15—19	96	40	41.67 ± 5.03
20—24	173	80	46.24 ± 3.79
25—29	114	28	24.56 ± 4.03
30—34	60	14	23.33 ± 5.46
35—39	50	6	12.00 ± 4.60
40—44	41	6	14.63 ± 5.52

tion 0.18. The normal variations accordingly are small, ranging between 0 and 1.04. Readings in excess of 1.2 must be considered as definitely pathological. Table 4.

The Hijman van den Bergh's test during the stage of incubation.

On account of preliminary preparations the work was not started until Jan. 26th. In the meantime 12 persons had been taken ill. The serumbilirubin readings during the course of clinically manifest disease having been elucidated earlier it was decided to discontinue testings after the onset of jaundice. 37 individuals either refused to have tests taken or were in such an agitated state of mind

Table 4.

Distribution of Hijman v. den Bergh's readings (= H v B) in 99 healthy persons. N = number of observations.
Mean = 0.49 ± 0.02 . Median = 0.5. Standard deviation = 0.18.

H. v. B.	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1
N	1	21	17	17	21	14	5	—	2	1

that it could not be done. Accordingly only 104 persons could be tested at, on average, six days' intervals. The total number of tests examined was 794 only 55 of which were obtained from persons

Table 5.

Serumbilirubin figures according to Hijman v. den Bergh's direct and indirect tests (1/200.000) at 6 days intervals before and after the falling ill of 25 hepatitis cases in Sörfors. n = number of observations. $M \pm \epsilon (m)$ = mean \pm standard error of the mean.

Days before (—) and after (+) onset of jaundice	Hijman v. den Bergh's test					
	indirect 1/200.000		direct			
	n	$M \pm \epsilon (m)$	% neg.	% faint trace	% trace	% pos.
—35 to—30	4	1.06 ± 0.26	100			
—29 to—24	3	1.18 ± 0.06	100			
—23 to—18	7	1.44 ± 0.39	85.7			14.3
—17 to—12	11	1.43 ± 0.09	90.9	9.1		
—11 to—6	15	1.11 ± 0.12	100			
—5 to \pm 0	15	2.63 ± 0.68	26.6	6.7	13.4	53.3
+ 1 to+ 7	7	4.58 ± 0.96				100

who subsequently developed jaundice. The results are recorded in Table 5 from which it will be learnt that definitely pathological amounts of bile pigments are found in serum 3—4 weeks before the

Table 6.

Number of Hijman v. den Bergh's indirect tests carried out at, on an average, 5 days intervals in 79 member of the Strömsör population who did not show any signs of clinical illness or jaundice.

N = number of tested persons, n = number of tests.

n	N	Product
1	8	8
2	2	4
3	2	6
4	—	—
5	1	5
6	3	18
7	1	7
8	1	32
9	6	54
10	6	60
11	17	187
12	23	273
13	6	78
Total	79	732

onset of jaundice indicating the liver to be involved already during the first fortnight after infection. The general trend of the readings is one of gradual increase. The departure from this rule, observed in the second week before onset of illness, might perhaps be interpreted as due to the rhythmic nature of all processes in the liver. The struggle between morbid and reparative forces might entail phases of reverses as well as of progredient deterioration.

The direct tests show a tendency to fluctuate in harmony with the indirect readings but a definite lagging behind is noticeable. which should indicate the liver cell to be primarily attacked, the bile capillaries becoming involved at a later stage.

The Hijman van den Bergh's test in clinically healthy persons exposed to infection.

At the outset of the epidemic between 30 and 50 cases were anticipated while the bulk of the population could be expected to escape the disease. The great number of bloodtests deriving from this unaffected majority were originally intended to serve as

material for determining the normal range of readings. It soon became obvious, however, that elevated serum bilirubin figures constituted a frequently occurring phenomenon, rendering the tests unsuitable for the estimation of what should be considered as normal. See Tables 6 and 7.

The observation that 69 out of 79 (or 87.34 ± 3.74 %) clinically healthy individuals showed definitely pathological concentrations

Table 7.

Maximal. Hijman v. den Bergh's readings (= H. v. B.) in 79 persons of the Strömsör population who did not show clinical signs of illness or develop jaundice. N = number of persons in the respective groups.

H. v. B.	N	H. v. B.	N
0.8	1	2.1	1
1.0	2	2.2	3
1.1	3	2.3	1
1.2	4	2.4	1
1.3	5	2.5	1
1.4	13	3.0	1
1.5	10	3.2	1
1.6	10	3.3	1
1.7	4	3.5	2
1.8	4	4.0	1
1.9	5	4.5	1
2.0	3	5.0	1

of serumbilirubin seems to be of considerable interest, indicating a rate of susceptibility not previously suspected. Not only does this discovery support the theory of »healthy carriers» propounded by Wallgren but some idea is given of their number in certain circumstances. 'Silent hepatitis' of the type found during the stage of incubation and among the contacts during an epidemic must be considered to indicate an accumulation of contagion in the livers with consequent excretion of virus via the bile.

During an outbreak we accordingly have to reckon with a greater number of »carriers» than of actually sick persons. Effective isolation of all suspects in the environment of a case of hepatitis being impracticable the only preventive measure likely to have any effect

on the spread of the disease should be improved sanitation with particular stress laid on water hygiene.

There is no noticeable correspondance between the Hijman van den Bergh readings and manifest jaundice. On the one hand we find serumbilirubin figures of between 2 and 4 on the day when jaundice was first observed whilst, on the other hand we see corresponding or even higher values in persons who never became icteric.

Summary.

The author reports on 2 outbreaks of epidemic hepatitis in the adjoining districts of Bjurholm and Nordmaling in the S. E. corner of the county of West Bothnia and produces evidence in support of the opinion that they were interrelated and that the Öre river, serving as recipient to the Bjurholm focus and source of water supply to the Sörfors asylum in Nordmaling, transmitted the infection.

The greatest *epidemiological* interest is attached to the outbreak taking place in the asylum for feeble minded in Sörfors with a population of 150 persons, among whom 34 came down with the disease, representing a morbidity of 22.7 %. The age distribution was ascertained in the whole population as well as among the hepatitis cases enabling a conception regarding the susceptibility at different ages. Significant differences were not established between the morbidities in the different 5 years' periods but the figures are too small to admit of general conclusions. By combining the simliar materials from the two institutional outbreaks in Hällnäs and Strömsör sufficiently large figures become available to warrant the assertion that epidemic hepatitis is not more common among children or adolescents than among persons in the 3rd and 4th decades. In more advanced ages the morbidity gradually decreases.

The *clinical* investigation was aimed at discovering how early in the stage of incubation the liver becomes involved, as indicated by serumbilirubin increase. To this end the largest possible number of the exposed population were subjected to bloodtests at, on the average, 6 days intervals, employing the Hijman van den Bergh method.

Primarily it was found necessary to establish the normal range of the test by examining a sufficient number of healthy persons.

As a result of this side issue the mean value was found to be 0.49 ± 0.02 . The standard deviation being 0.18 the normal range lies between 0 and 1.04. Readings in excess of 1.2 must be considered as definitely pathological. Applying this touchstone to the series of observations obtained from 22 patients on various days before their developing jaundice it was found that indications of the liver being involved could be traced already 3—4 weeks before the disease was clinically manifest. Comparison of the readings obtained by the indirect and direct tests respectively seem to suggest the liver cells to sustain damage in the first place, the bile capillaries becoming subsequently affected. An analysis of the great number of tests derived from 79 persons who never showed any signs of the disease revealed pathological concentrations of serum-bilirubin in no less than 69 cases or 87 %. This discovery supports the theory of »healthy carriers» and its consequences with regard to preventive action are briefly touched upon.

Aknowledgment.

It is my pleasant duty to express my sincere gratitude to Mr. G. Wigren, secretary to the County Council, by whose intercessions necessary personnell was placed at my disposal, Sven Ekvall, director of the general hospital in Umeå who extended to me the hospitality of his laboratory, miss Ingeborg Odenstam the responsible head of the laboratory. who kindly undertook to impart the required technique to my assistant and controlled her work, the district medical officers Olof de Val and M. Lagerlöf who willingly contributed valuable information and, not least to my wife, Mrs Asta Hallgren, who has carried out all the tests with the meticulous precision characteristic of all her activities.

I also want to thank sincerely Mr. John Keenan for his kindness in perusing my manuscript and correcting the apparently inevitable solecisms.

The Rigshospital, Copenhagen.

Spermatogenesis in a eunuchoid man, 32 years old, after four years of hormone therapy.

By

P. PLUM.

(Submitted for publication April 2, 1943).

According to the literature accessible to me, all previous attempts to establish the production of sperm cells in an adult eunuchoid have turned out unsuccessful. So the following case history may be of some interest.

The patient consulted me in autumn 1938, nearly 4 ½ years ago. He was then 28 years old and wanted to know whether there might be any possibility of an effective treatment of the defective development of his genitals.

Case Record.

Past History. — Since puberty he had realized that his genital development was abnormally slight, and gradually he was becoming more and more unhappy about his shortcoming. From the age of puberty to the institution of treatment he had experienced only an occasional suggestion of any sexual desire, and he had had a suggestion of erection only a few times. He had never had any ejaculation.

He had never shaved himself. His voice was not markedly childish. Mentally he was well balanced, and fairly resigned to his fate. He stated that he tired readily; but he was able to attend to his work in the shops of Burmeister & Wain. Further, he was sensitive to cold to an annoying extent.

At the age of 15 years he was operated on for a severe attack of appendicitis with perforation. Subsequently a small hernia developed in the scar.

At the age of 19, on his way home from South America, he and the rest of the ship's crew had a severe attack of psittacosis.

Physical Examination, in autumn 1938: Through the kindness of Professor Warburg, I had the patient admitted to the Medical Dep. B, the Rigshospital. His appearance is evident from Figs. 1 and 2, which show a typical picture of eunuchoidism: very long extremities and feminine proportions. Further, extremely poor development of the genitals, the penis measuring about 2 cm. Scrotum not pendulous, with the testes located at a high level, about the size of a nut kernel or a small almond. Pubes extremely scanty; no growth of beard; thin eyebrows. Complexion pale. Skin of the face wrinkled as in an elderly woman. Prostate not palpable with certainty.

Height: 169 cm. Weight: 56.5 kg, that is, about 10 kg under the normal weight for his height and age.

Other clinical examinations revealed no abnormality; in particular, ophthalmoscopy showed normal conditions.

Laboratory Examinations. — Urine: No albumin or sugar; no abnormal elements on microscopy; diuresis and specific gravity normal. Hemoglobin: 105 %. Blood pressure: 130/85. Wassermann negative. Sedimentation rate: 5 mm/1 hr; Mantoux negative. Basal metabolism: 98 %. Serum calcium: 10.5 mg %. Bexelius' test: No petechiae. Electrocardiography: No abnormality.

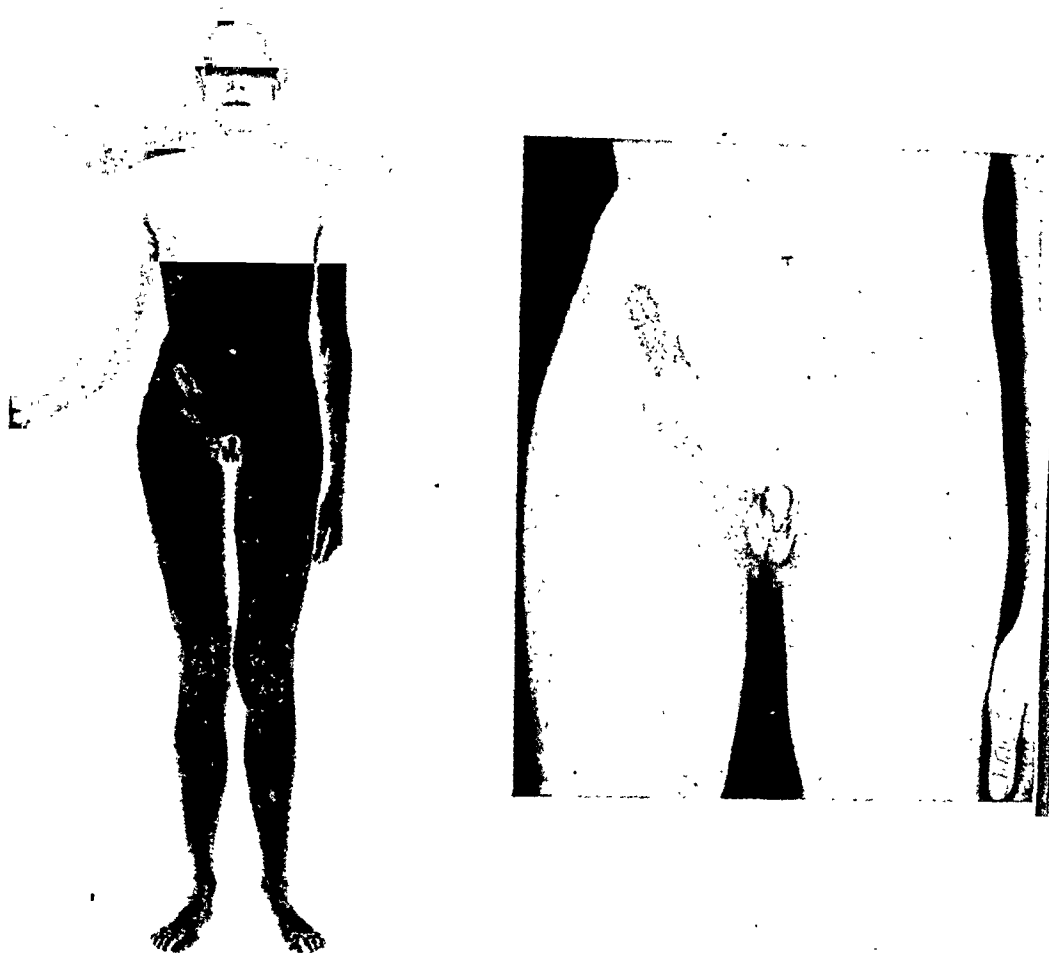
X-ray Examination: Sella turcica presents a peculiar flattened form, measuring 11 mm in length, 5 mm in depth; the surface area, 55 sq. mm, is distinctly below the normal minimum for his age, which is stated to be 69 sq. mm. The long bones show persistent epiphyseal lines in the radius, ulna, the distal part of the tibia and the head of the femur, that is, a distinctly delayed ossification, which is typical of eunuchoids and eunuchs.

Hormonal Analysis: Presence of small amounts of gonadotrophic hormone, testicular hormone and estrin.

Treatment and Course. — After operation for the small ventral hernia (in the Surgical Dep. D) the hormone therapy was commenced in December 1938, that is, a little over four years ago.

The treatment consisted partly in gonadotropic hormone, partly testicular hormone. To begin with, the patient was given injections of Physex (gonadotropic hormone prepared from the urine of pregnant women), 1500 I. U. twice a week, which for a brief interval was replaced by Antex (gonadotropic hormone prepared from the serum of pregnant mares), 750 I. U. twice a week.

After 9 months of treatment the patient had for the first time an ejaculation, but otherwise his improvement was slight, subjectively as well as objectively. In the following 8 months he was treated with injections of testicular hormone (Perandren), 25 mg twice a week. Under this treatment there was a considerable growth of the genitals, the patient had for the first time a sensation of sexual desire, and in May 1940, after treatment for 1 ½ years, he had coitus for the first time. Repeated examinations showed no sperm cells in the ejaculate. From July 1940 to March 1942 he was given



Figs. 1 and 2. Eunuchoid, 28 years old, prior to the institution of treatment.

rather small doses of Physex, Antex and Testex (testicular hormone) in order to maintain the result obtained. In the middle of this period, May 1941, he was married, and he stated that his married life proceeded normally. In June 1942 we decided to try to obtain an additional improvement and increased the dosage of Physex to 1500 I. U. three times a week. After 4 months of this treatment the testes were growing considerably, measuring now 3×2.5 cm, and examination of the semen showed 48,000 sperm cells per ejaculate, most of which cells were not motile. (These examinations were kindly carried out by Dr. Hammen.) After additional 4 months of intensive treatment with Physex, ejaculation of sperm became regular, and now the examination showed 1.5 million sperm cells per ejaculate.



Figs. 3 and 4. Appearance of the patient after 4 years' treatment.

The patient is exceedingly satisfied with his present condition. His chilliness is all gone. He now looks upon his sexual life as quite normal. The change in his appearance is evident from Figs. 3 and 4.

In the course of 4 years he has received altogether 377 injections of hormonal preparations: 200 injections of Physex, 62 Antex, and 103 of testicular hormone.

The hormonal preparations were kindly placed at my disposal by »Løvens kemiske Fabrik» and, to a small extent, »Ciba». The total cost for the purchase of these preparations would have amounted to 2064 Danish kroner.

While it is a well-known thing that it is quite possible by means of testicular hormone to produce growth of the genitals and an increase in the sexual desire and potency in persons with genital hypoplasia as well as in

normal subjects, as mentioned before, I have not been able to find any record of a case of an adult with pronounced eunuchoidism in whom an attempt to set the sperm production a-going turned out successfully.

As the course of the affection in this case may reasonably be said to imply the chance that the sperm cells under continued treatment may become normal quantitatively and perhaps also qualitatively, it will be rational to continue the treatment with gonadotropic hormone. Undoubtedly, it will be advisable to withhold the employment of testicular hormone preparations, as animal experiments and clinical experiences have shown that these preparations decrease the number and motility of the sperm cells.

Whether Antex or Physex has played the greater rôle in the result obtained, is difficult to say. The decisive improvement in the last three-quarters of a year took place under the Physex treatment. Theoretically, one would expect an additional improvement from the administration of Antex, which exerts a particular influence on the spermatogenesis, while Physex acts especially on the interstitial tissue of the testes.

Summary.

A man, 28 years old, suffering from eunuchoidism is treated for 4 years with gonadotropic hormone and testicular hormone. After 9 months' treatment ejaculation is recorded; after $1\frac{1}{4}$ years sexual desire makes its appearance, followed 3 months later by potency. After $2\frac{1}{2}$ years the patient gets married, and after nearly 4 years of treatment sperm cells appear in the ejaculate.

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(Chief: Professor C. E. Bloch, M. D.)

Relation between Prothrombin Concentration and Clotting Time.¹

By

P. PLUM.

(Submitted for publication May 3, 1943).

The question about the relation between the prothrombin concentration and the clotting time is of practical interest as well as theoretical. The present work will deal with the practical significance of this problem to the methods for determination of the prothrombin content of the blood.

The mode of action of the thrombin has been a subject of considerable discussion. At present, however, it is almost generally agreed that thrombin is of enzymatic nature. Hence, the quantitative estimation of the enzyme has to be carried out after the same principles as the measuring of other enzymes which cannot be determined by purification and weighing, namely: by estimating the activity of its specific effect under certain conditions. As the only specific function of thrombin is coagulation of fibrinogen its coagulative capacity has to be estimated on a solution of fibrinogen or plasma. For this, two ways are open: either determine how rapidly a given specimen of thrombin can induce coagulation, or examine how much the specimen has to be diluted in order to give coagulation at a certain point of time. Concerning the hitherto available methods after the first-mentioned principle, in 1910 Wohlge-

¹ These studies were carried out with the aid of a grant from the Rockefeller Foundation and from King Christian X's Jubilee Fund.

muth (27) said: »so haben sie doch alle den Nachteil, dass man mit ihnen nur die Gerinnungszeiten bestimmen kann und nicht die in gleichen Zeiten umgesetzten Substanzmengen. Derartige Methoden sind aber an sich nicht geeignet, das Wirkungsgesetz eines Fermentes zu ermitteln, noch viel weniger gestatten sie Rückschlüsse auf die Fermentquantitäten, solange die Gesetzmässigkeit der Fermentwirkung noch nicht bekannt ist». Wohlgemuth therefore worked out a method for measuring of thrombin based on the last-mentioned principle — dilution of the specimen — until the dilution gives clotting at a certain point of time, as he took for granted that a certain amount of thrombin corresponds to a certain clotting time.

Recent investigations have shown that the rule of direct proportionality between the amount of enzyme and the rate of reaction applies to nearly all enzymes examined, provided that the specimen is free from impurities or inhibiting substances. This has been demonstrated to apply to pepsin, for instance, by Northrop (10) (1920). *A priori*, then, it would be reasonable to assume that the same regularity holds good of thrombin.

Several investigators have looked into this question and their results have turned out to be fairly uniform. Nevertheless, in the literature opinions differ on this point because some of the previous experiments were not carried out with thrombin but with a tissue extract which previously was assumed to have a thrombin effect, and which, we now realize, has the effect of a kinase, *i. e.*, it promotes the formation of thrombin from the inactive prothrombin.

These experiments [in particular those reported by Fuld (4) 1902] have continuously given rise to confusion, as even more comprehensive works on the subject [*e. g.*, Wöhlisch (28, 29)] fail to differentiate sharply between thrombin experiments and kinase experiments.

A survey of the results obtained by various investigators is given in Table 1. From this, I think, the results may be said to have been fairly uniform: within a certain range of thrombin concentration there is a direct proportionality between the thrombin concentration and the rate of coagulation. The experiments are carried out either with solutions of purified fibrinogen or with plasma. For thrombin the investigators have used either dilutions of serum or preparations of purified thrombin.

Table 1. Relation between Thrombin Concentration and Rate of Coagulation.

Author	Year	Source of thrombin	Fibrinogen substrate	Clotting time	Relation between thrombin concentration and rate of coagulation
Loeb ⁸	1907	Serum	Lobster plasma	5 min.-50 min.	Direct proportionality
Mellanby ⁹	1909	Purified thrombin	Purified fibrinogen	7-120 sec.	Direct proportionality
Rettger ¹⁶	1909	Purified thrombin	Purified fibrinogen	14-90 sec.	Direct proportionality
Stromberg ²⁰	1911	Purified thrombin	Purified fibrinogen	Min. to 32 hours	Direct proportionality within a limited range
Tsunoo ²³	1925	Purified thrombin	Fibrinogen and plasma	60-900 sec.	Direct proportionality within a limited range
Bleibtreu ¹	1926	Purified thrombin	Plasma	10-125 sec.	Direct proportionality
Eagle ³	1935	Purified thrombin	Fibrinogen	60-150 sec.	Approximate proportionality; but clotting time increasing a little less than degree of dilution
Quick ¹⁵	1936	Purified thrombin	Fibrinogen and plasma	0-80 sec.	Approximate proportionality; but clotting time increasing a little less than degree of dilution
Wöhlisch, Diebold & Kiderlen ³⁰	1936	Purified thrombin	Fibrinogen	0-15 sec.	Direct proportionality
Herbert ⁵	1940	Purified thrombin	Fibrinogen	0-120 sec.	Approximately direct proportionality
Plum	1943	Purified thrombin	Plasma	5-270 sec.	Direct proportionality within a limited range

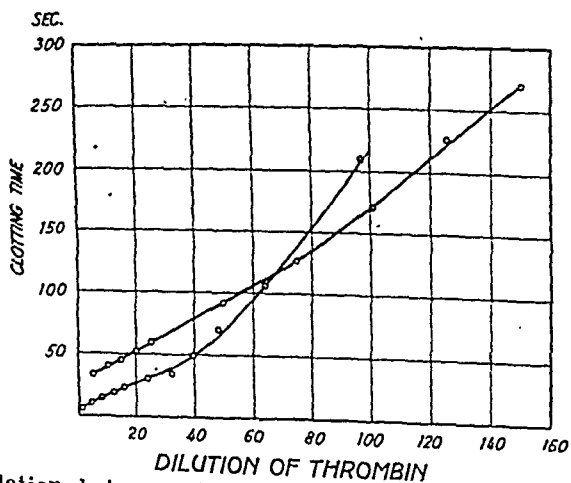


Fig. 1. Relation between, thrombin concentration and clotting time.

Fig. 1 shows two such experiments in which the thrombin was a purified and very active preparation (0.1 cm^3 of a 1 % thrombin solution coagulated 0.1 cm^3 of human plasma in 5 seconds), and the substrate was prothrombin-free human plasma (prothrombin by aluminium hydroxide). As is evident from Fig. 1, within a certain range the relation between the degree of dilution and the clotting time was linear, while on higher dilution the clotting time increases relatively more than the degree of dilution.

According to the above, it may be considered established that — at any rate within a certain range of concentration — there is a direct proportionality between the thrombin concentration and the rate of coagulation. In the clinic, however, we wish to determine the prothrombin concentration of the plasma, not the amount of thrombin. As is well known, the process of coagulation takes place through the activation of prothrombin into thrombin by a tissue factor — thrombokinase — together with calcium ions, and then the thrombin brings about a transformation of fibrinogen into fibrin. This effect of thrombin is counteracted by antithrombin, which normally is present in the plasma. Even though the time for the action of thrombin be known, then, it does not tell us anything definite about the relation between the prothrombin concentration and the clotting time, as the prothrombin first has to be activated into thrombin, and this thrombin is in some degree inactivated by the antithrombin of the plasma. So far the literature has brought but very scanty reports concerning studies on this question, which obviously is important when it comes to judge of the results of a prothrombin determination — especially when a comparison is to be made of results obtained with different methods for prothrombin determination.

The available methods for prothrombin determination are based on three different principles: 1) Quick's principle (13) (1935), which consists in determination of the clotting time for recalcinated oxalate plasma after addition of an excessive amount of kinase, the clotting time being taken as a measure for the prothrombin concentration; 2) Warner, Brinkhous & Smith's principle (24) (1936), which — like Wohlgemuth's (27) method from 1910 — is based on the supposition that, under established conditions, a certain amount of prothrombin corresponds to a certain clotting time; and 3) Schönheyder (17, 18) Dam-Glavind's (2) principle, which is based on the

observation that plasma with a low prothrombin content can be brought to clot just as rapidly as plasma with a normal prothrombin concentration when the added amount of kinase is increased; the amount of kinase required for clotting at a certain time is thus an expression for the prothrombin concentration. Schönheyder (19) (1938) has shown that the method is tenable as far as avian blood is concerned, while it is not so suitable for mammalian blood as the two first-mentioned principles; and hence it will not be discussed further here.

After Wohlgemuth-Warner, Brinkhous & Smith's principle two similar methods have been worked out — by Thordarson (21, 22) (1939) and by Herbert (5) (1940). From the above it is evident that with these two methods the presupposition for obtaining values corresponding to the actual prothrombin content of the plasma is: that a certain amount of prothrombin corresponds to a given clotting time. If normal plasma in dilution 1: 100 gives a clotting time, *e. g.*, of 8 minutes, and a plasma with an abnormal prothrombin content in dilution 1: 10 likewise gives a clotting time of 8 minutes, the prothrombin concentration of the latter plasma should be 10 % of the normal. But this has not been proved to hold true.

In methods after Quick's principle attempts have been made in various ways at a »standardization» with establishment of the relation between the prothrombin percentage in proportion to the normal and the clotting time (»prothrombin time»). As emphasized already, these methods cannot stand criticism, and the same applies to the procedure described by Larsen & Plüm (6): addition of known amounts of normal blood to various specimens of blood with low prothrombin concentration — in order, by this means, to obtain a curve from which it might be practicable from the clotting directly to read the prothrombin percentage.

A few authors [*e. g.*, Lehmann (7)] have evaded the problem by setting up the concept »prothrombin index», that is

$$\frac{\text{prothrombin time on normal blood, in sec.}}{\text{prothrombin time on the abnormal blood, in sec.}} \times 100.$$

In a previous paper (12) it has been pointed out that this index does not correspond to the prothrombin percentage, and that it is dependent on the thrombokinas preparation employed and on the Quick modification employed.

As is evident from the above, then, the problem is, whether Wohlgemuth's principle is founded on a correct supposition, and whether it is possible in methods after Quick's principle to give a serviceable procedure for calculation from the clotting time to the actual amount of prothrombin (in relation to the normal). Presumably, both these problems would have been solved if, as in the case of thrombin, the time relation for prothrombin were known — *i. e.*, the relation between the rate of reaction and the amount of proenzyme.

In the present work an attempt is made to solve this question in three different ways.

A. It might seem obvious to look into the time aspects of prothrombin in the same way as has been done in the case of thrombin, by analysis of the clotting times for various dilutions of a purified prothrombin preparation. No such attempt was made, however, as it would not be justified from this to draw any direct conclusion about the conditions in the blood or plasma dilutions employed in the prothrombin methods. So, another way was chosen: A number of specimens of blood with very different prothrombin contents are diluted in a certain proportion — 1: 2 and 1: 4. Then the clotting times obtained for the undiluted sample of the blood and for the dilution are plotted as one point in a coordinate system, so that the point read on the ordinate gives the clotting time for the undiluted sample, and the point read on the axis of abscissas gives the clotting for dilution 1: 2. In the same coordinate system the values obtained for dilutions 1: 2 and 1: 4 are plotted, so that dilution 1: 2 is read on the ordinate, dilution 1: 4 on the abscissa.

Owing to the unavoidable error of the method, the plotted points show a certain range of variation. But a line can be drawn through these points, and this line turns out to be straight over a fairly long section, running so that dilution 1: 2 within the linear section of the curve gives a clotting time of twice the clotting time for the undiluted sample, that is, there is direct inverse proportionality between the prothrombin concentration and the clotting time, or direct proportionality between the prothrombin concentration and the rate of coagulation.

These determinations were carried out in part with Plum & Dam's (11) modification of Quick's method, partly with Larsen & Plum's (6) modification. In Plum & Dam's modification Ringer's

fluid is used as diluent, so that one dilution contained 0.2 cm^3 blood + 0.1 cm^3 Ringer's fluid, the other 0.1 cm^3 blood + 0.2 cm^3 Ringer's fluid. In the experiments carried out with Larsen & Plum's modification, the total volume and the total amount of citrate are kept constant. The amount of NaCl is adjusted so that the diluent in all dilutions is isotonic with the blood. As mentioned, the amount of blood varies from 0.2 cm^3 to 0.05 cm^3 .

One might imagine that the resulting curve (Figs. 2 and 3) in part would be an accidental product of the technique employed — in particular, that the varying amount of fibrinogen would influence the form of the curve. This can be excluded, however, as the points resulting from determination of dilutions 1:1 and 1:2 and the points resulting from employment of dilutions 1:2 and 1:4 fall on the same line. Furthermore, the circumstance, that the result obtained with the original modification (Plum & Dam) practically corresponds completely to the result obtained with the later modification (Larsen & Plum), suggests very strongly that prothrombin here is the only decisive factor, as the two modifications employed differ rather considerably: Plum & Dam's method employs non-stabilized blood and room temperature, whereas Larsen & Plum's modification employs recalcinated citrate blood and water-bath at 37° . With both methods the transformation of prothrombin into thrombin is activated by an optimal amount of kinase. The blood is capillary blood obtained from a lively bleeding cut in the heel, a new cut being made for each sample of blood.

Table 2. *Clotting Time (Prothrombin Time) determined on Various Dilutions (4:2:1) of Blood from Experimental Subjects with Differing Prothrombin Content of the Blood.*

Capillary blood (C) Venous blood (V)	Experimental subject	Clotting time (prothrombin time) in sec. with employment of		
		0.2 cm^3 of blood	0.1 cm^3 of blood	0.05 cm^3 of blood
V	Parturient	11.7	15.2	22.0
V	Parturient	12.8	17.3	23.2
V	Normal adult	13.3	17.5	29.8
C	Newborn	19	30.5	59
C	Newborn	21	39	65
C	Newborn	43	77	168
C	Newborn	112	264	540
C	Newborn	230	462	810
C	Newborn	338	785	2160

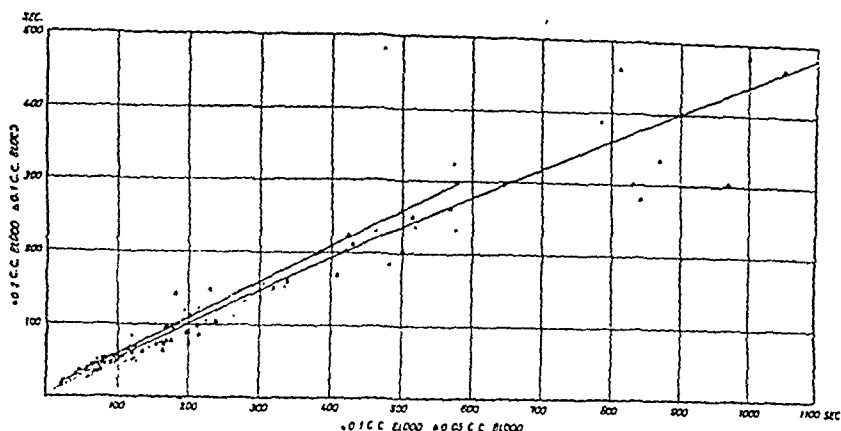


Fig. 2. Influence of the dilution on the prothrombin time examined on 175 children with differing prothrombin content of the blood (for the sake of space only about 140 points are plotted here). Each point read on the ordinate gives the prothrombin time on employment of 2 parts blood; read on the abscissa it gives the prothrombin time on employment of 1 part blood. The circles indicate experiments with employment of 0.2 cm³ of blood in one test (ordinate) and 0.1 cm³ of blood in the other test (abscissa). The triangles indicate experiments with employment of 0.10 cm³ and 0.05 cm³ of blood. The total volume is kept constant. The experiments marked with circles and triangles are carried out after Larsen & Plum's method. The upper line, marked X, is plotted on the basis of 50 experiments performed in a similar way but with Plum & Dam's technique for determination of prothrombin.

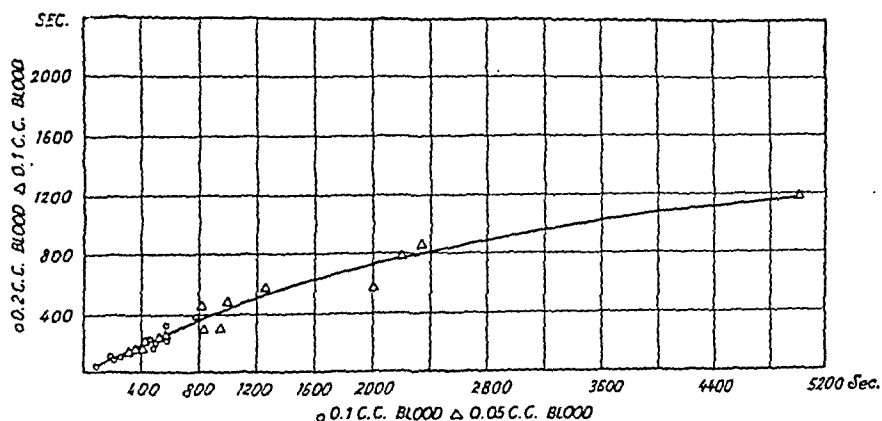


Fig. 3. Same as Fig. 2, but drawn at a smaller scale, in order to include also the very long prothrombin times.

A few of the mentioned determinations are recorded in Table 2, from which, as well as from Figs. 2 and 3, it will be seen that the direct proportionality is observed only within a certain range, corresponding to a clotting time of between about 30 and 500 sec., whereas the clotting time below this level increases less than proportionally to the dilution, and over this range it increases more than corresponding to a direct proportionality.

As the relation between thrombin concentration and clotting time is constant, and as the relation between prothrombin concentration and clotting time — as just demonstrated — is found to be rectilinear, we may conclude that the same must apply to the activation time of prothrombin, as the activation time plus the clotting time for the thrombin gives the total prothrombin time. In order to see whether this may be confirmed experimentally, an experiment was carried out after the method given by Warner, Brinkhous & Smith (24, 26) as this method differentiates between the two phases of the coagulation: activation of prothrombin and coagulation of fibrinogen by the thrombin found.

For practical reasons the method was modified on a few points. Instead of adding a solution of fibrinogen after the activation of prothrombin, citrate plasma was used. This citrate plasma contains sufficient citrate ($\frac{1}{10}$ volume of 10 % sodium citrate) to prevent the added amount of calcium from inducing coagulation. The specimen of blood to be analyzed was taken with $\frac{1}{10}$ volume of 3 % sodium citrate; the blood corpuscles were separated from the plasma, to which was added 1 drop of a 4 % thrombin suspension per cm^3 of plasma, by which the fibrinogen was precipitated and brought to contraction by shaking with glass beads. The added amount of thrombin is inactivated by the plasma antithrombin in about 15 minutes. Then a series of dilutions of the fibrinogen-free plasma was made; the diluent employed for this was a mixture of citrate and NaCl adjusted so that the citrate concentration was kept approximately constant, and the dilutions were continually isotonic with the blood (0.6 % sodium citrate in 0.65 % NaCl). Now, to 0.1 cm^3 of each dilution was added 1 drop of thrombokinase suspension [Dam & Glavind (2)] and 0.025 cm^3 of 0.6 % CaCl_2 , $2\text{H}_2\text{O}$. Activation as well as coagulation were carried out in water-bath at 37° . Now the optimal activation time is determined for each dilution — by determining at which activation time the shortest clotting time was obtained on addition of 0.1 cm^3 of the above-mentioned plasma taken with 10 % citrate. The clotting times observed for each dilution and the corresponding optimal activation times are presented graphically in Fig. 4.

From Fig. 4 it will be noticed that the experiment here performed showed a linear course of the relation between dilution and activation time as well as between dilution and clotting time

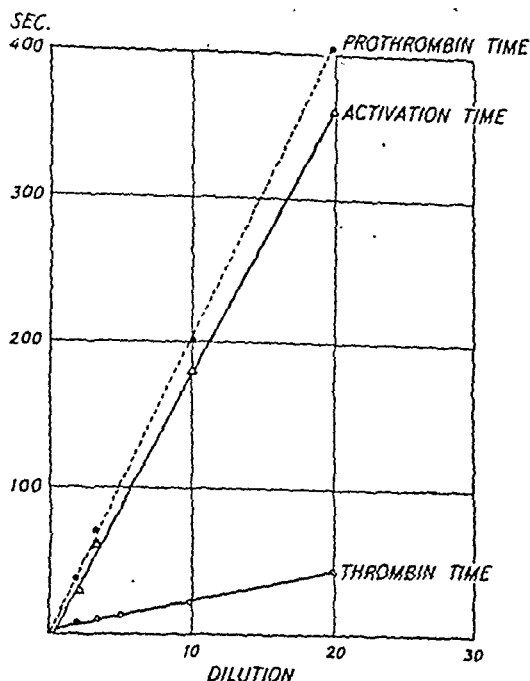


Fig. 4. Relation between plasma dilution and activation time and clotting time (thrombin time) in a slightly modified 2-step method after Warner, Brinkhous & Smith's principle.

(thrombin time). Addition of the activation times and clotting times for the individual dilutions gives the upper line which naturally must be straight, too — as was to be expected.

This experiment affords an explanation of why the time relation for the action of thrombin is the same as for that of prothrombin. The experiment further shows, as has been pointed out also by other authors [*e. g.*, Eagle (3); Warner, Brinkhous & Smith (24, 26); Thordarson (22)] that the activation of prothrombin into thrombin makes up by far the greater part of the total clotting time (prothrombin time).

B. From the above considerations and experiments the conclusion must be that within a certain range of concentration the prothrombin time gives a direct measure for the prothrombin concentration. In order to test the correctness of this conclusion, in a fundamentally different way, some experiments were made after Thordarson's method. This method may be said to be based on Wohlgemuth's principles and also on Quick's, the prothrombin time being determined on the number of plasma dilutions of normal blood and patient blood without differentiation of the two phases

of coagulation. Now a curve is drawn for the coagulation times in the various dilutions of each specimen, and the calculation is carried out as follows: At a suitable point on the curve (where its direction changes from a more horizontal course to a more vertical) the time is selected — for instance, 5 minutes — and it is noted which dilution of the normal blood and of patient blood gives clotting in this length of time. If, for instance, it is found for the normal blood to be a 3 % dilution, and for the patient blood the 6 % dilution, the calculation is: $\frac{3 \times 100}{6} = 50$ % of the normal.

The test was modified so that prothrombin-free plasma (absorbed by aluminium hydroxide) was employed instead of a solution of fibrinogen; this plasma has the advantage of keeping better and being considerably easier to prepare. Instead of lung extract, human brain extract is used for thrombokinese (Dam & Glavind). The method was further modified so as to be suitable for capillary blood, which is not the case with the original method.

From a lively bleeding cut in the heel, 0.5 cm³ of blood is withdrawn into a micro-test tube containing 0.5 cm³ of medinal buffer solution with oxalate. Thordarson's medinal buffer solution is employed with addition of 0.2 % potassium oxalate. The blood is at once mixed thoroughly with the oxalate-medinal buffer solution and this mixture is used for the dilutions wanted, the same oxalate-medinal solution being employed as diluent. Thus whole blood is used instead of plasma.

With Thordarson's method experiments were now made on a number of subjects with normal prothrombin content or with decreased prothrombin content of the blood. Instead of plotting the percental prothrombin content along the axis of abscissas — as done by Thordarson — the degree of dilution was plotted directly *i. e.*, the number of cubic centimeters to which 1 cm³ of blood is diluted. If the theory about the direct proportionality between prothrombin concentration and clotting time holds true, we should find that 1) the clotting times for the various dilutions lie on a straight line with the inclination differing according to the prothrombin content; and 2) the calculation of the prothrombin percentage should turn out alike whether we employ the aforementioned calculation after Thordarson (clotting times of the same length), or we use a calculation starting from dilutions of the same degree (*i. e.*,

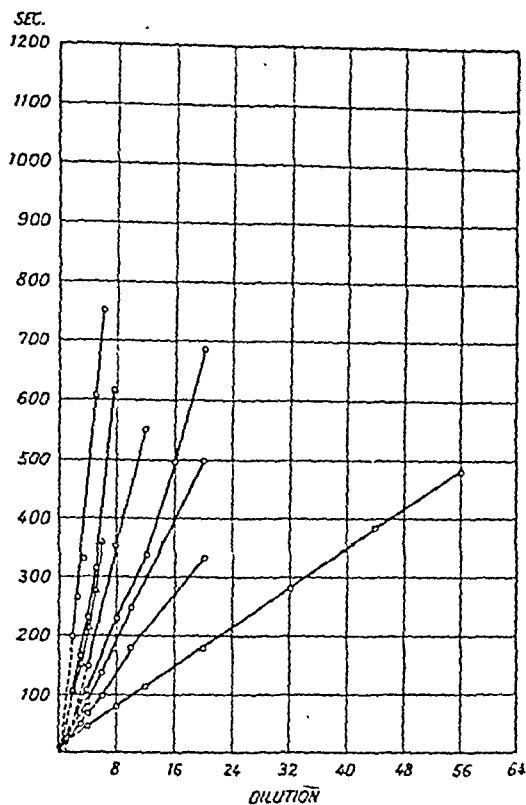


Fig. 5. Determinations of the clotting time carried out on increasing dilutions of blood from persons differing in their prothrombin content, after a modification of Thordarson's method.

if the normal blood clots, in dilution 1: 10 in 100 sec., and patient blood coagulates in 200 sec. the calculation is: $\frac{100 \times 100}{200} = 50 \%$ of the normal.

As is evident from Fig. 5 and from Tables 3, 4 and 5, this turned out to be the case.

As seen from Fig. 5, in all experiments the curve was rectilinear for a fairly long distance. Furthermore, the curves come very near showing a direct proportionality between the degree of dilution (*i. e.*, the prothrombin concentration) and the clotting time.

For the sake of illustration, two of the experiments are recorded in Table 3.

If now we calculate the prothrombin content of the blood for the two children in percent of the prothrombin content of a normal adult, calculation after the two principles will give us the following results:

Table 3. *Two Prothrombin Determinations on Children with Lowered Prothrombin Content of the Blood. Modification of Thordarson's Method.*

Dilution of the blood	Blood percentage of dilution	Clotting time in sec.		
		Normal subject	Child 1417	Child 1396
1: 4	25.0	45	105	148
1: 8	12.5	78	230	352
1: 12	8.34	113	340	550
1: 16	6.25	145	495	695
1: 20	5.00	180	685	1115
1: 32	3.12	280	—	—
1: 44	2.27	382	—	—
1: 56	1.78	480	—	—

Table 4. *Calculation ad modum Thordarson of the Prothrombin Determinations recorded in Table 3.*

Time selected	Prothrombin in percentage of the value found for the normal subject	
	Child 1417	Child 1396
150 sec.	$\frac{6.15}{19.8} \times 100 = 31.1 \%$	$\frac{6.15}{25.0} \times 100 = 24.6 \%$
200 sec.	$\frac{4.45}{14.5} \times 100 = 30.7 \%$	$\frac{4.45}{20.0} \times 100 = 22.2 \%$
300 sec.	$\frac{2.9}{9.35} \times 100 = 31.0 \%$	$\frac{2.9}{14.4} \times 100 = 20.1 \%$
450 sec.	$\frac{1.9}{6.65} \times 100 = 28.6 \%$	$\frac{1.9}{10.2} \times 100 = 18.6 \%$
Average	30.4 %	21.4 %

Table 5. *Calculation of the Prothrombin Determinations recorded in Table 3, from the Prothrombin Times in Identical Dilutions of the Blood.*

Dilution	Prothrombin in percentage of the value observed in the normal subject	
	Child 1417	Child 1396
1: 8	$\frac{78}{230} \times 100 = 33.9 \%$	$\frac{78}{352} \times 100 = 22.2 \%$
1: 12	$\frac{113}{340} \times 100 = 33.2 \%$	$\frac{113}{550} \times 100 = 20.5 \%$
1: 16	$\frac{145}{495} \times 100 = 29.3 \%$	$\frac{145}{730} \times 100 = 20.8 \%$
Average	31.2 %	21.2 %

Ad modum Thordarson we find, after plotting of the three curves (which for want of space are not reproduced here), the values recorded in Table 4.

If we calculate the prothrombin content of the blood in the children, taking for granted that at a certain dilution there is inverse proportionality between the clotting time and the prothrombin concentration (or direct proportionality between the prothrombin concentration and the rate of coagulation), we find the values recorded in Table 5.

Tables 4 and 5 show good agreement between the two methods of calculation; they further show that calculation after either method alone gives nearly the same result even if it is carried out on the basis of different clotting times, or different solutions.

The experiments cited here as mere examples picked out among a good many concordant experiments, thus show that within a certain prothrombin concentration range there is direct proportionality between the rate of coagulation and the prothrombin concentration.

C. Finally, I have tried in two fundamentally different ways to plot a curve showing the relation between the prothrombin time determined ad modum Larsen & Plum and the prothrombin percentage. One procedure consisted in plotting such a curve on the basis of the experiments recorded in Figs. 2 and 3, taking the normal value to be about 17.5 sec. and setting the prothrombin value as 100 % of the normal. The curve shows that 17.5 sec. on the ordinate corresponds to about 27 sec. on the abscissa, that is, a prothrombin content amounting to one-half of the normal will give this prothrombin time: The plotting is continued in the same manner: 27 sec. on the ordinate corresponds to 45 sec. on the abscissa; accordingly, blood with one quarter of the normal prothrombin content (or 25 %) should give a prothrombin time of 45 sec., and so on. A curve calculated and plotted in this way is shown in Fig. 6.

The other procedure consisted in determining the prothrombin content on a number of subjects (adults and newborn) by means of the modified Thordarson method described and after Larsen & Plum's method. The results obtained ad modum Thordarson, expressed in per cent of the normal, are plotted against the corresponding prothrombin times determined ad modum Larsen & Plum, so that the percental values are read on the abscissa, the prothrombin times on the ordinate. As is evident from Fig. 6, the

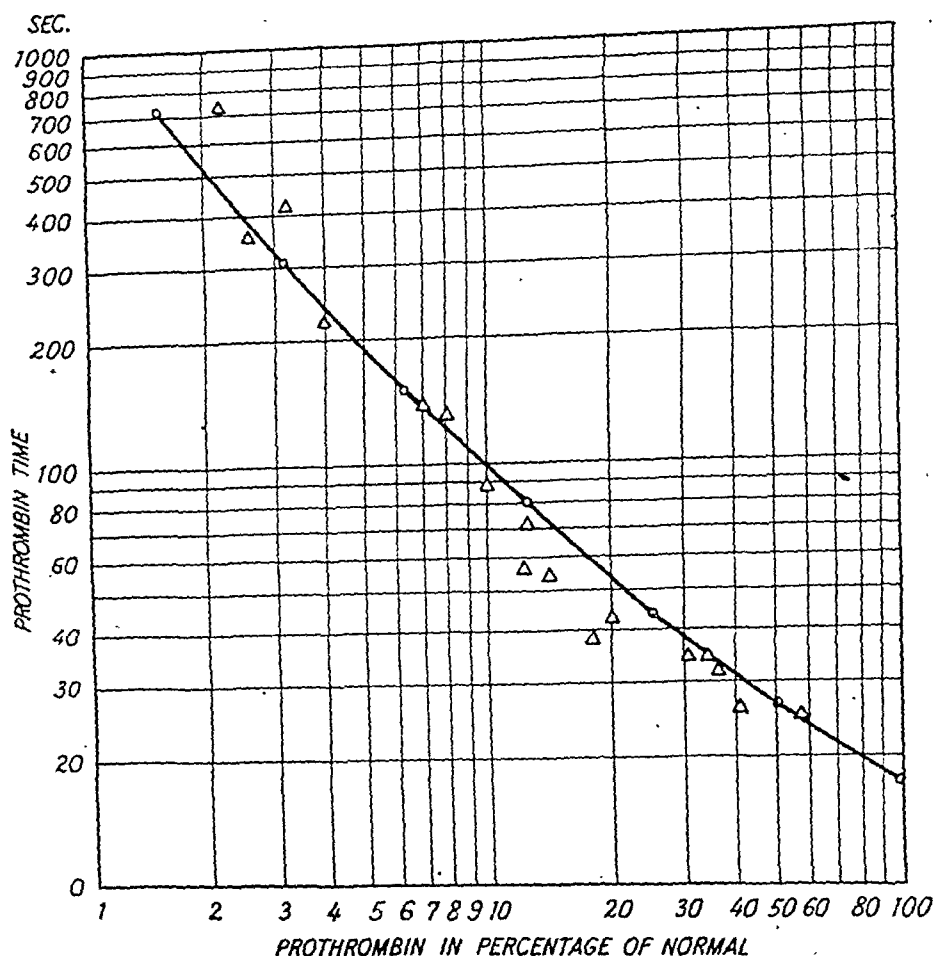


Fig. 6. Curve for the relation between prothrombin concentration and prothrombin time, constructed on the basis of the experiments recorded in Figs. 2 and 3. Each Δ signifies an experiment in which the prothrombin content is determined after Thordarson's method, slightly modified (reading on the abscissa) and after Larsen & Plum's method (reading on the ordinate).

results obtained show fairly good agreement, indicating that both the procedures employed are justified.

Summary.

1. Knowledge of the time relation for the action of prothrombin is of decisive importance to the evaluation of methods for prothrombin determination.

2. On the basis of the literature and the writer's studies there is shown within a certain range of concentration to be direct proportionality between thrombin concentration and rate of coagulation.

3. Experimentally, in fundamentally different ways the same law of time is shown to apply to the action of prothrombin.

4. A modification of Thordarson's method is given, the fibrinogen being replaced by absorbed plasma. Further, this method is modified so that instead of requiring 5 cm³ of blood now 0.5 cm³ is sufficient. Capillary blood from the heel has proved serviceable for this purpose.

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Aus dem Gesundheitsamt der Stockholmer Studentenschaften (Vorstand: Dr. C. Gentz) und der Medizinischen Klinik des Karolinischen Krankenhauses, Stockholm (Vorstand: Prof. N. Svartz).

Zur Frage der tuberkulösen Primärinfektion bei jungen Erwachsenen.

Von

S. BERGQVIST und T. ERNBERG.

(Bei der Redaktion am 24. März 1943 eingegangen).

Einleitung.

Die früher herrschende Ansicht verlegte die tuberkulöse Primärinfektion fast regelmässig in die Kindheit. Durch eine Reihe von Untersuchungen ist indessen nachgewiesen worden, dass diese Anschauung nicht mit dem wirklichen Sachverhalt im Einklang steht. Es scheint im Gegenteil immer häufiger zu werden, dass die Erstinfektion nicht vor dem Eintritt in das Erwachsenenalter erfolgt. Mehrere, namentlich skandinavische Autoren haben sich eingehend mit der Primärinfektion des Erwachsenen, dem Verlauf derselben sowie ihrer Bedeutung für eine spätere Tuberkulose beschäftigt (Heimbeck, Arborelius, Scheel, Malmros und Hedvall, Kristenson, Holm u. a.). Eine ausführliche Zusammenfassung des einschlägigen Schrifttums ist kürzlich von Kristenson veröffentlicht worden. Wir halten es für gerechtfertigt, über eine neue Serie ähnlicher Untersuchungen zu berichten, da gewisse Fragestellungen, welche in diesem sowohl theoretisch wie praktisch wichtigen Zusammenhang Interesse besitzen, eine weitere Beleuchtung verdienen dürften. Gewiss wird es wohl in unserem Lande — zumindest in absehbarer Zeit — infolge der grossen Verbreitung, welche die

BCG-Schutzimpfung schon heute hat und vermutlich auch in Zukunft haben wird, kaum möglich sein, neue derartige Reihenuntersuchungen durchzuführen. Es wird immer schwerer werden, tuberkulinnegative, nicht schutzgeimpfte Personen während eines längeren Zeitraums zur Beobachtung zu erhalten. Unser Material ist verhältnismässig gross und durch Röntgenaufnahmen konsequent und eingehend verfolgt worden.

Methodik.

Im Gesundheitsamt der Stockholmer Studentenschaften sind seit 1934 Tuberkuloseuntersuchungen an Studierenden sämtlicher Stockholmer Hochschulen im Gange gewesen. Seit Eröffnung des Gesundheitsamts im Herbst 1934 sind bis einschliesslich Frühjahrssemester 1941 rund 7000 Studenten und Studentinnen registriert und wenigstens einmal untersucht worden. Bei etwa der Hälfte von diesen wurden eine oder mehrere Nachuntersuchungen vorgenommen, je nach Art des Falles in kürzeren oder längeren Zwischenräumen. So wurden Tuberkulinnegative wie Tuberkulinpositive mit Befund mehrere Male jährlich kontrolliert. Bis zum Ende des Frühjahrssemesters 1941 sind 6629 Studierende in bezug auf Tuberkulinproben und Röntgenbilder vollständig durchuntersucht worden. Unter vollständiger Untersuchung verstehen wir Tuberkulinproben bis zur Dosis 1 mg sowie Durchleuchtung und Frontalaufnahme. Ausserdem wurden bei allen sorgfältige Anamnesen erhoben, namentlich natürlich mit Rücksicht auf frühere tuberkulöse Affektionen, ferner auf familiäres Vorkommen tuberkulöser Krankheiten und spezielle Ansteckungsmöglichkeiten. Überdies wurde gleichzeitig mit jeder Röntgenaufnahme die Senkungsreaktion angestellt.

Während der Zeit Herbstsemester 1934 — Beginn des Herbstsemesters 1935 wurde bei der Tuberkulinuntersuchung die Pirquet'sche Reaktion (mittels Impfbohrers) als erste Probe verwendet, danach die Intrakutanprobe (Mantoux) mit 0.1 und 1 mg. Nach diesem ersten Jahr wurde indessen die Pirquetsche Probe aufgegeben und die Intrakutanprobe nach Mantoux (im folgenden abgekürzt: Mantoux) ausschliesslich verwendet, wobei als erste Dosis 0.1 mg gegeben wurde und später erforderlichenfalls 1 mg. Um die heftigen Reaktionen zu vermeiden, welche bisweilen nach 0.1 mg als erste Probe auftraten, wurde 1937 als erste Dosis 0.01 mg einge-

führt, zunächst mit Beibehaltung der Proben mit 0.1 und 1 mg. Seit 1938, wo die Zwischenprobe mit 0.1 mg aufgegeben wurde, ist auf die erste Injektion von 0.01 mg, wenn die Reaktion negativ war, unmittelbar ein erneuter Mantoux mit 1 mg gefolgt. Dieses vereinfachte Verfahren hat ausschliesslich gute Erfahrungen geliefert. Eine Tuberkulinprüfung erfordert also höchstens drei Besuche im Gesundheitsamt, ein Vorteil sowohl für die Klientel wie für das Amt, namentlich im Hinblick darauf, dass es erwünscht ist, die Tuberkulinnegativen zu möglichst dicht aufeinanderfolgenden Kontrollen heranzuziehen.

Das Tuberkulin wurde aus dem Staatlichen Bakteriologischen Laboratorium bezogen und die Verdünnung in einer Apotheke ausgeführt, wobei wöchentlich neues Tuberkulin geliefert wurde. Als positive Pirquetsche Probe wurde eine Reaktion von mindestens 5×5 mm Rötung und Infiltrat betrachtet, als positiver Mantoux eine wenigstens 10×10 mm grosse Rötung mit Infiltrat. Beide Reaktionen wurden nach 48—72 Stunden abgelesen.

Diejenigen Studierenden, welche bei 1 mg negativ gewesen waren, wurden mit wiederholten Tuberkulinuntersuchungen laufend kontrolliert. Bei eventuellem Positivwerden wurde eine erneute genaue Anamnese erhoben, mit besonderer Berücksichtigung der Ansteckungsmöglichkeit, und ferner wurde eine neue Röntgenuntersuchung und neue SR vorgenommen. Die Röntgenuntersuchung bestand da aus Durchleuchtung und Aufnahmen in sowohl sagittaler wie frontaler und wenn nötig auch schräger Richtung. Bei der Beurteilung der Bilder von frisch Positiven war es von ausserordentlichem Wert, dass das Gesundheitsamt immer über bereits bei der ersten Untersuchung, bei welcher der Patient tuberkulinnegativ gewesen war, aufgenommene Röntgenbilder verfügte. Diese frisch Positiven wurden dann im allgemeinen während der nächsten Jahre einige Male in jedem Semester zu regelmässigen Röntgenuntersuchungen und zur SR wiederbestellt.¹

Material.

Von rund 7000 Studierenden sind 6629 vollständig teils in bezug auf den Röntgenbefund (Durchleuchtung und Aufnahme) und

¹ Die Deutung der Röntgenbilder besorgten die Röntgenologen des Gesundheitsamts, Herr Dr. K. B. Jäderholm (bis 1938) und Herr Privatdozent Dr. med. G. Jönsson (von 1939 an).

Tabelle 1.

Verteilung der bei der ersten Untersuchung Tuberkulinnegativen auf Hochschulen und Altersgruppen.

Hochschule	A l t e r								Sa.	Gesamt- zahl	Prozent Tuberkulin- neg.
	17—18	18—20	20—22	22—24	24—26	26—28	28—30	>30			
Stockholmer Hochschule	6	127	118	32	15	4	—	—	302	2028	14.9
Technische „	2	82	96	40	8	2	—	—	230	1667	13.8
Medizinische „	—	53	47	21	7	2	1	—	131	968	13.5
Handels- „	1	14	27	16	2	3	—	—	63	575	11.0
Odontologische „	—	18	43	17	8	4	—	—	90	508	17.7
Pharmazeutische „	—	1	17	44	10	4	2	—	78	503	15.5
Veterinär- „	—	3	15	1	1	—	—	—	20	184	10.9
Forsthochschule, Sozialpolit. Inst. u. Kunstakademie ..	—	1	3	12	4	—	1	—	21	196	10.7
Sa. Tuberkulinnegative ...	9	299	366	185	55	19	4	—	935	6629	14.1
Gesamtzahl Untersuchte	52	1732	2348	1341	558	309	122	167	6629		
Prozent Tuberkulinnegative ..	17.3	17.3	15.6	13.6	9.8	6.2	3.3	0			

Tabelle 2.

Schwedische Tuberkulinuntersuchungen an erwachsenen Jugendlichen aus verschiedenen Orten und Bevölkerungskreisen.

Autor	Material	Prozent Tuberkulin- negative
Arborelius (1927—29)	Militärdienstpflichtige, mit Ausnahme der Landbewohner	13.5±0.8
Bergqvist u. Ernberg (1934—41)	Studierende, Stockholm	14.1±0.4
Malmros u. Hedvall (1930—37)	Studierende und Lehrschwestern, Lunc	18.3±0.7
Sjövall (1934—36) ..	Studierende, Upsala	24.2±0.9
Arborelius (1927—29)	Militärdienstpflichtige, reine Land- bewohner	35.3±1.1

teils hinsichtlich der Tuberkulinreaktion (Mantoux bis 1 mg) untersucht worden. Von diesem Material waren bei der ersten Untersuchung 935 negativ, d. s. 14.1 ± 0.43 v. H. Die Verteilung derselben auf die verschiedenen Altersgruppen und Hochschulen wird aus Tab. 1 ersichtlich. Wie man sieht, sinkt die Zahl der Nega-

tiven mit höherem Alter, so dass schon in der Altersgruppe 28—30 Jahre von 122 Studierenden nur 4 negativ waren, d. s. 3.3 v. H. In Tab. 2 sind zum Vergleich schwedische Tuberkulinuntersuchungen an erwachsenen Jugendlichen aus verschiedenen Orten und Bevölkerungskreisen zusammengestellt

Zur Beleuchtung von Faktoren, welchen man einen Einfluss auf die Zusammensetzung der Gruppe bei der ersten Untersuchung Negative, die hier besonderes Interesse besitzt, zuschreiben könnte, seien folgende Zahlen angeführt (Tab. 3): Der Prozentsatz Negative unter Studierenden mit Tuberkulose in der Familie (Eltern und Geschwister) ist 9.8. Diejenigen Studierenden, bei welchen Tuberkulosefälle nur in der Verwandtschaft (wir sind hierbei nicht weiter gegangen, als bis zu den Grosseltern, Onkeln und Tanten) vorgekommen sind, haben eine etwas höhere Anzahl Negative, nämlich 12.6 v. H., und die ohne Tuberkulose in der Familie oder Verwandtschaft die höchste Zahl, 14.7 v. H. Die Differenz zwischen diesen letztgenannten und der ersten Gruppe mit Tuberkulose in der Familie beträgt 4.9 v. H. und ist statistisch sicher. Die Zahlen sind freilich nicht überraschend; immerhin verdient die Tatsache Beachtung, dass so viele wie 9.8 v. H. aus Familien, in denen Eltern oder Geschwister an tuberkulösen Erkrankungen gelitten hatten, im Erwachsenenalter noch immer negativ sind (es sei allerdings dar-

Tabelle 3.

	Anzahl	davon Prozent Neg.	Differenz
Gesamtmaterial	6629	14.1±0.4	—
Männer	5280	13.3±0.5	
Frauen	1349	17.1±1.0	3.8±1.1
Keine Tbc. in Familie od. Verwandtschaft	5535	14.7±0.5	
Tbc. in Verwandtschaft (Grosseltern, Onkels u. Tanten)	422	12.6±1.6	2.1±1.7
			4.9±1.2
Tbc. in Familie (Eltern u. Geschwister)	672	9.8±1.1	2.8±1.9
In Stockholm geboren	2049	15.8±0.8	
Im übrigen Lande geboren	4580	13.3±0.5	2.5±0.9
In Stockholm wohnhaft	2635	15.3±0.7	
Im übrigen Lande wohnhaft	3994	13.3±0.5	2.0±0.9

auf hingewiesen, dass die Krankheit der Angehörigen mitunter schon vor der Geburt des Untersuchten abgelaufen gewesen war). Die im Erwachsenenalter Negativen stellen indessen doch gewissermassen eine Auslese von Individuen ohne familiäre Belastung dar, ein Sachverhalt, der, wie man aller Wahrscheinlichkeit nach annehmen kann, allgemeine Geltung besitzt.

Die Verteilung der Tuberkulinnegativen auf das männliche und das weibliche Geschlecht ist 13.3 bzw. 17.1 v. H., mit einer Differenz, welche statistisch gesichert ist. Auch andere Untersucher (z. B. Long und Seibert) haben einen höheren Negativitätsprozentsatz für Frauen gefunden. Das Durchschnittsalter der Studenten und Studentinnen im Material beträgt 22.0 bzw. 21.9 Jahre. Da sich die Differenz in der Tuberkulinnegativität der Geschlechter weder durch den Altersunterschied, noch durch andere eventuelle Ungleichmässigkeiten der Auswahl erklären lässt, muss hier ein wirklicher Unterschied vorliegen, der offenbar bedeutet, dass die Frauen in jüngeren Jahren einer Tuberkuloseansteckung in geringerem Grade ausgesetzt sind als die Männer. Es sei auch erwähnt, dass ein statistisch sicherer Unterschied zwischen den einzelnen Hochschulen bezüglich der Anzahl der Negativen (Tab. 1) nicht vorliegt, wenn die Alters- und Geschlechtsverteilung berücksichtigt wird.

Betrachtet man die Zahlen für in Stockholm geborene bzw. heimatisierte Studierende im Vergleich zu den aus dem übrigen Lande, so findet man in beiden Fällen, dass die Stockholmer Studenten in grösserem Umfang tuberkulinnegativ sind. Die Differenzen sind jedoch nicht statistisch sicher. Eine Berechnung des Alters der in Stockholm und im übrigen Lande geborenen ergibt ausserdem, dass die ersteren im Durchschnitt ein Jahr jünger sind, nämlich 21.3 Jahre gegenüber 22.3 Jahre bei den letzteren. Wird der Negativitätsprozentsatz mit Rücksicht auf den Altersunterschied korrigiert, so bleibt doch eine höhere Negativitätszahl für die in Stockholm geborenen bestehen, welche allerdings zum Teil darauf beruhen dürfte, dass das weibliche Geschlecht etwas mehr vertreten ist. Der Negativitätsprozentsatz kann also in den beiden Gruppen als praktisch gleich hoch angesehen werden. Im allgemeinen hat man ja bei Untersuchungen dieser Art einen wesentlich niedrigeren Negativitätsprozentsatz für Grossstadtbevölkerung als für sonstige Volkskreise gefunden. Dass das Studentenmaterial in dieser Beziehung grössere Einheitlichkeit zeigt, ist indessen nicht über-

raschend. Einmal sind alle als Städter, wenigstens vom Alter von 10 Jahren an, d. h. von der Zeit, wo sie sich in einer Stadt mit höherer Lehranstalt aufhalten müssen, zu betrachten, sodann dürfte das soziale Milieu bei den beiden Gruppen gleichartig sein und schliesslich ist der Bevölkerungsaustausch zwischen der Hauptstadt und dem übrigen Lande ein lebhafter. Der letzte Punkt wird davon illustriert, dass 38 v. H. der in Stockholm ansässigen Studierenden in anderen Landesteilen und 10 v. H. der im übrigen Lande beheimateten in Stockholm geboren waren.

Aus vorstehendem wird mithin ersichtlich, dass die Gruppe der im Erwachsenenalter Tuberkulinnegativen im Vergleich zum Gesamtmaterial bis zu einem gewissen Grade eine Auslese von Frauen und von Individuen ohne familiäre Belastung verkörpert, dass sich aber sonst keine wesentliche Über- oder Unterrepräsentation konstatieren liess. Dass die Tuberkulinnegativen ein niedrigeres Durchschnittsalter aufweisen als die bereits bei der ersten Untersuchung Positiven, geht ohne weiteres daraus hervor, dass der Positivitätsprozentsatz mit steigendem Alter höher wird. So sind die Tuberkulinnegativen 21.1 Jahre alt, während das durchschnittliche Alter der Positiven 22.1 Jahre ist.

Von den 935 bei der ersten Untersuchung Negativen waren bei erneuten Tuberkulinproben 251 positiv geworden. Von den restlichen 684 stellten sich 208 nicht zur neuerlichen Kontrolle ein und sind also nur einmal mit Mantoux bis 1 mg untersucht und da negativ befunden worden. Unter den nur einmal Untersuchten befinden sich mehrere, bei denen die erste Untersuchung erst vor kurzem stattgefunden hat, sowie solche Studierende, die in andere Universitätsstädte übersiedelt sind. Bei einem Teil derjenigen mit kurzer Beobachtungszeit handelt es sich um Studierende, die bereits am Zeitpunkt der ersten Untersuchung vor dem Abschluss ihrer Studien gestanden hatten. Wir haben keinen Grund zu der Vermutung, dass derjenige Teil des Materials, welcher nur kurze Zeit unter der Kontrolle des Gesundheitsamts gestanden hatte, besonders zahlreiche Tuberkulosefälle aufweisen würde. Da das Gesundheitsamt Röntgenaufnahmen von allen Untersuchten besitzt und deshalb sowohl Krankenhäuser wie Privatärzte bei neu eintreffenden Erkrankungsfällen die früheren Platten leihweise anfordern, hat das Amt gute Möglichkeiten, den weiteren Schicksalen seiner früheren Klientel zu folgen.

Primärinfektionen ohne tuberkulöse Veränderungen.¹

Von 935 zunächst Tuberkulinnegativen mit negativem Röntgenbefund bei erster Untersuchung und mit negativer Anamnese unterzogen sich 727 erneuter Kontrolle, bei der, wie erwähnt, 251 positiv geworden waren, und bei 34 von diesen traten tuberkulöse Manifestationen auf. Aus Tab. 4 geht die Verteilung der 217 frisch Positiven ohne tuberkulöse Veränderungen auf die

Tabelle 4.

Verteilung von 217 frisch Positiven ohne primäre oder spätere tuberkulöse Veränderungen auf die einzelnen Hochschulen sowie in bezug auf die Beobachtungszeit nach dem Positivwerden.

Hochschule	Beobachtungszeit nach dem Positivwerden in Jahren						Sa.
	0	<1	1—2	2—3	3—4	4—5	
Medizinische Hochschule	2	9	13	9	13	2	48
Stockholmer „	3	19	15	15	7	—	59
Technische „	3	9	17	14	7	—	50
Odontologische „	3	10	10	3	5	2	33
Handels- „	4	6	—	—	—	—	10
Veterinär- „	—	1	2	3	—	—	6
Pharmazeutische „	2	3	2	1	—	—	8
Forst- „	—	2	—	—	—	—	2
Sozialpolit. Inst.	—	1	—	—	—	—	1
Sa.	17	60	59	45	32	4	217

einzelnen Hochschulen unter Berücksichtigung der Beobachtungsdauer nach dem Positivwerden hervor. Obwohl die Beobachtungszeit nach dem Positivwerden in gewissen der 217 Fälle kurz ist, dürften wahrscheinlich keine überhaupt sichtbaren Primäraffekte unentdeckt geblieben sein. Es ist nämlich wohlbekannt und geht aus veröffentlichten Reihenuntersuchungen, z. B. der Kasuistik von Malmros und Hedvall, klar hervor, dass der Primäraffekt, wenn er überhaupt sichtbar wird, in relativ nahem Zusammenhang mit dem Positivwerden auftritt. Bezüglich der Möglichkeit einer später auftretenden Lungen tuberkulose, m. a. W. der weiteren Prognose

¹ In E. . . . eines besseren Ausdrucks haben wir die eingetragte Bezeichnung verwendet, obwohl es im Hinblick auf die Erfahrungen der letzten Jahre über die Instabilität der Tuberkulinreaktion (Dahlstrom u. a.) als wahrscheinlich erachtet werden kann, dass dieselbe bei einem Teil dieser Fälle nicht adäquat ist.

dieser frisch Infizierten oder latenten Infektionen (Arborelius), ist die Beobachtungszeit in vielen Fällen nicht lang genug, um ein allgemeingültiges Urteil zu gestatten. Von 140 Fällen, bei welchen die Beobachtungszeit ein Jahr überstieg, waren jedoch 59 1—2 Jahre, 45 2—3 Jahre, 32 3—4 Jahre und 4 schliesslich 4—5 Jahre lang nachuntersucht worden.

In einer vorangehenden Arbeit hatten wir nachgewiesen, dass die Tuberkulinempfindlichkeit in einem Material von röntgennegativen Gesunden im dritten Lebensjahrzehnt mit steigendem Alter zunimmt, wobei wir annahmen, dass diese Allergiesteigerung auf wiederholte latente exogene Infektionen zurückzuführen wäre. Die grössere Tuberkulinempfindlichkeit der Älteren würde m. a. W. darauf beruhen, dass diese mehr Infektionen ausgesetzt gewesen waren, welche, ohne eine tuberkulöse Manifestation auszulösen, doch die allergische Reaktion des Organismus verstärkt hatten. Bei einem Material von frisch positiven Gesunden ohne röntgenologische Veränderungen oder andere tuberkulöse Manifestationen konnte man daher einen niedrigeren Allergiegrad erwarten als bei einem Vergleichsmaterial, welches aus gesunden, früher infizierten Personen besteht. In dem hier beschriebenen Material bestätigt sich diese Annahme. Von den 217 Fällen reagierten beim Positivwerden 47 v. H. bei Mantoux mit 0.01 mg positiv, der Rest erst bei grösserer Dosis. Bei unserer obenerwähnten Untersuchung hatten wir für eine dem durchschnittlichen Alter der frisch Positiven entsprechende Gruppe unter schon bei der ersten Untersuchung Positiven eine Reaktion auf 0.01 mg in über 70 v. H. der Fälle gefunden, welche sämtlich ganz gesunde röntgennegative Individuen waren. Es ist also offenbar, dass eine Primärinfektion, welche keine Erkrankung veranlasst, in vielen Fällen mit einer schwachen oder mässigen Allergie einhergeht. Auch Malmros und Hedvall haben bei Primärinfizierten in vielen Fällen eine relativ schwache Allergie festgestellt. So reagierten in dem Material derselben (151 Primärinfektionen bei Erwachsenen) 52 v. H. auf Pirquet, weitere 25 v. H. auf Mantoux mit 0.1 mg und 23 v. H. auf Mantoux mit 1 mg.

Primärinfektionen mit tuberkulösen Veränderungen.

Unter denjenigen 251 Negativen, welche tuberkulinpositiv wurden, traten bei 34 Anzeichen einer tuberkulösen Manifestation auf.

Tabelle 5.

Die tuberkulösen Erscheinungen der Primärinfizierten bei der Feststellung der Krankheit (ohne Berücksichtigung später hinzukommender Veränderungen).

Hochschule	Erythema nodosum	Pleuritis	Hilus- Lymphom	Primär- komplex		Veränder- ungen nur im Lun- genparen- chym	Sa.
				in der Lunge	aus- serh. d. Lunge		
Medizinische Hochsch.	1	3	2	3	1	4	14
Odontologische „	1	—	—	2	—	1	4
Technische „	—	3	1	2	—	1	7
Veterinär- „	—	1	—	—	1	—	2
Stockholmer „	—	—	—	—	—	—	—
(Humanisten u. Juristen)	1	—	2	2	—	1	6
Handels- „	—	—	1	—	—	—	1
Sa.	3	7	6	9	2	7	34

Von diesen 34 waren 14 Mediziner. Die Verteilung auf die Lehrfächer ergibt sich aus Tab. 5. Bei drei Fällen handelte es sich um Erythema nodosum, in allen bei Frauen, bei zwei um Lymphdrüsentuberkulose im Anschluss an eine Obduktionsverletzung der Hand und bei sieben um Pleuritiden. Was Affektionen der Lunge betrifft, so kamen neun Fälle mit gleichzeitigem Lungen- und Hilusbefund vor, sechs Fälle mit lediglich Hilusveränderungen sowie schliesslich sieben mit Lungenparenchymherden, von welchen wahrscheinlich nicht alle als primär aufzufassen sind (Tab. 6).

Stellt man die Zeit fest, welche zwischen der letzten negativen und ersten positiven Tuberkulinreaktion vergangen war, so findet man, dass diese im Durchschnitt bei etwa sechs Monaten liegt, dass sie aber in dreizehn der Fälle höchstens drei Monate beträgt. Bei einem Falle lässt sich der Zeitpunkt genau angeben, an welchem der Umschlag eintrat.

K. L., Cand. med., geb. 1915, war bei Mantoux mit 1 mg zuletzt am 13. X. 1939 tuberkulinnegativ gewesen. 20. XI. 1939 Mantoux mit 0.01 mg positiv, wobei Pat. angab, dass eine Woche zuvor an der Stelle der letzten Injektion (1 mg) eine 10 × 10 mm grosse Rötung aufgetreten war. Er hatte seit zwei Monaten an Obduktionen teilgenommen und sich bei einer solchen vor einem Monat am linken Ringfinger geschnitten. Diese Wunde war noch nicht verheilt. 20. XI. 39 Status: Über der Grundphalanx des

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Ringfingers der linken Hand eine gerötete und infiltrierte Partie, in der linken Achselhöhle eine gut haselnussgrosse Lymphdrüse. Röntgenbefund der Lungen negativ. SR 2 mm/st. Subfebril. Am 1. XII. 39 wurde auch eine Drüse in der linken Cubitalregion konstatiert. Exzision dieser Drüse, pathologisch-anatomische Diagnose: Adenitis tbc. Finsenbehandlung, dabei allmähliche Heilung der Wunde. Im April 1941 jedoch neue Drüsen-schwellung in der linken Axilla. Röntgenuntersuchung der Lungen am 27. IV. 42: o. B.

Bei den drei Fällen mit Erythema nodosum traten während der Beobachtungszeit keine Lungenveränderungen oder sonstige Anzeichen einer tuberkulösen Erkrankung auf. Bei einem derselben (1) stellte sich indessen nach einem Jahr ein Rezidiv ein. Bei einer (10) der vier rechtsseitigen Pleuritiden wurden zwei Jahre später kleinere fleck- und streifenförmige Verschattungen im ersten Intercostalraum rechts entdeckt. Von den übrigen mit Exsudat auf der linken Seite (7, 9, 12) bekam einer (7) später ein Rezidiv auf der anderen Seite, und einer (9) hatte Tuberkelbazillen im Sputum, ohne dass sich ein Parenchymherd nachweisen liess.

Bei fünf (13, 14, 15, 16, 17) von den sechs Fällen mit lediglich Hilusveränderungen nahm das Röntgenbild wieder das normale Aussehen an, und in einem Fall (18) ist der Hilus nach einer Beobachtungsdauer von 12 Monaten noch immer deformiert. In drei (23, 25, 26) von den neun Fällen mit vollständigem Primärkomplex erfolgte eine restlose Rückbildung. Bei Fall 20, wo sowohl die Lungen- als auch die Hiluskomponente geringen Umfang hatte, trat während einer Beobachtungszeit von 26 Monaten im Aussehen derselben keine Veränderung ein. Bei einem Fall (22) verkleinerte sich sowohl die Lungen- wie die Hiluskomponente erheblich. In einem Fall (24) entwickelte sich etwa einen Monat nach der Entdeckung auf derselben Seite eine Pleuritis, und in einem anderen (27) entstand auf derselben Seite eine Parenchymverschattung hinter der ersten Rippe, eine Veränderung, deren Umfang im Laufe der dreijährigen Beobachtungszeit später beträchtlich abnahm. Bei einem Fall (19) trat ein Jahr später eine grossfleckige Parenchymverschattung unterhalb des rechten Hilus (wo sich die Lymphome verkleinert hatten), lateral vom Primärherd und im Anschluss an diesen auf. In einem Fall (21) schliesslich wurden neun Monate nach der Entdeckung des Primärkomplexes supraclaviculär und lateral im ersten Intercostalraum unscharf begrenzte Flecke entdeckt, die nach zwei Jahren plötzlich um sich griffen. Was das Aussehen der Lungenkomponente bei diesen neun Fällen von Primärkomplex anlangt, so war dasselbe, wie aus Tab. 7 ersichtlich wird, sehr wechselnd, sie schwankte von ganz geringfügigen Veränderungen bis zu grösseren, zusammenhängenden Parenchymverschattungen. Bei Fall 22 und 23 beispielsweise wurde die Erkrankung anfangs infolge der sehr beträchtlichen Ausdehnung des Primärkomplexes als Bronchopneumonie aufgefasst, ehe die Art des Leidens geklärt war.

Bei zwei Fällen mit Infiltration nur im Lungenparenchym entstand dieselbe zwei bis drei Monate nach negativer Tuberkulinreaktion und mit

Fall	Hochschule		Alter beim Erkranken	Geschlecht	Zeit zw. neg. u. pos. Tuberkulinfektion (Monate)	Zeit zw. pos. Tuberkulinfektion u. tuberkulöser Manifestation (Monate)	Diagnose beim Beginn der Krankheit
1	Stockholmer	Hochschule	22	♀	7	10 Tage	Erythema nodosum
2	Odontologische	»	20	♀	2 ½	0	» »
3	Medizinische	»	22	♀	24	1	» »
4	Veterinär-	»	23	♂	3	0	Ulcus man. dextr. c. lymphon. tbc. axill. dextr.
5	Medizinische	»	21	♂	1	0	Ulcus tbc. dig. IV man. sin. lymphom. reg. cubital. et axill. sin.
6	Veterinär-	»	21	♂	8	0	Pleuritis dextr.
7	Technische	»	22	♂	5 ½	0	» sin.
8	»	»	23	♂	12	12	» dextr.
9	»	»	21	♂	24	0	» sin.
10	Medizinische	»	26	♂	12	0	» dextr.
11	»	»	21	♀	2	0	» dextr.
12	»	»	22	♂	6	0	» sin.
13	Technische	»	21	♂	8	0	Hiluslymphom links
14	Stockholmer	»	23	♂	9	0	» »
15	»	»	21	♂	8 ½	0	» »
16	Medizinische	»	21	♂	2	0	» rechts
17	»	»	23	♀	3	0	» »
18	Handels-	»	20	♀	7	0	» »
19	Technische	»	23	♂	5 ½	0	Primärkomplex rechts
20	»	»	22	♂	16	0	» links
21	Stockholmer	»	20	♂	3	0	» »

Beobachtungszeit im Monaten n. Ent- deckg. der Mani- festation	Aussehen und Verlauf (vgl. Text und Tab. 7—8)	Heilstätten- oder Krankenhaus- aufenthalt
12	ein Jahr später Rezidiv. Lungenrtg. o. B.	—
35	Lungenrtg. o. B.	—
33	Lungenrtg. o. B.	+
38	Obduktionsverletzung der Hand, Wunde nach 1 ½ Monat geheilt. Exstirpation einer Lymphdrüse, pathologisch-anatomische Diagnose: Lymphoma tbc. Bakteriologische Untersuchung: Tuberkelbazillen, Typus bovinus.	—
30	s. Text.	—
16	zwei Monate später Rtg. o. B.	+
37	am Tage vor dem Erkranken Rtg. negativ! Zwei Jahre später Rezidiv rechts.	+
25	ein Jahr später Lungenrtg. o. B.	+
25	Tuberkelbazillen im Sputum, aber keine sichtbare Lungenveränderung	+
48	zwei Jahre später kleinere Parenchymverschattungen in I 1 rechts. Drei Monate zuvor Lungenrtg. negativ.	+
37	kurze Krankheitsdauer. Lungenrtg. o. B.	+
26	» » » »	+
24	Rtg. o.B. 8 Monate später.	+
20	» » 20 » »	—
41	» » 24 » »	—
50	» » 12 » »	—
30	» » 12 » »	—
12	erhebliche Rückbildung.	—
26	Hiluskomponente wird kleiner. Ein Jahr n. d. Erkr. in einem handtellergrossen Bezirk unter dem rechten Hilus, lateral vom Primärherd und im Anschluss an diesen grossfleckige Parenchymverschattung. Die Verschattung war auf dem Rtg.-Bilde 4 Mon. vorher nicht vorhanden. Pneumothorax. Prozess unverändert.	—
26	unverändert.	+
34	vollständige Rückbildung des Lungenherds 8 Mon. später. Nach einem weiteren Monat supraclaviculär, in I 1 und I 3 unscharf begrenzte Flecke, welche 2 Jahre später plötzlich um sich greifen.	—
		+

Fall	Hochschule	Alter beim Erkranken	Geschlecht	Zeit zw. neg. u. pos. Tuberkulinfektion (Monate)	Zeit zw. pos. Tuber- kulinfektion u. tuberkulöser Mani- festation (Monate)	Diagnose beim Beginn der Krankheit
22	Stockholmer Hochschule	21	♂	2	0	Primärkomplex links
23	Odontologische »	24	♂	4	0	» »
24	» »	21	♂	6	0	» rechts
25	Medizinische »	27	♂	6	0	» links
26	» »	22	♀	2 ½	0	» rechts
27	» »	23	♂	6 ½	0	» links
28	» »	22	♂	2	0	Parenchymveränderung links
29	» »	23	♂	1	2	» rechts
30	» »	25	♂	6	8	» links
31	» »	26	♂	3	3 ½	» »
32	Odontologische »	21	♂	7	10 ½	» rechts
33	Stockholmer »	21	♂	2 ½	28	» links
34	Technische »	21	♂	8 ½	10 ½	» rechts

einem Verlauf, der auch darauf hindeutet, dass die Veränderungen als Primärherde anzusehen sind (28, 29). Diese Deutung ist vielleicht noch bei zwei weiteren Fällen am Platze (30, 31). Fall 30: Im ersten Intercostralraum links gelegene, gut abgegrenzte, haselnuss-grosse, rundliche, homogene Verschattung, die beim Positivwerden nicht vorhanden war, sondern erst bei einer folgenden Röntgenuntersuchung acht Monate später entdeckt wurde. Die

p. (Fortz.)

Beobachtungszeit in Monaten n. Entdeckung der Manifestation	Aussehen und Verlauf (vgl. Text und Tab. 7—8)	Heilstätten- oder Krankenhaus-aufenthalt
32	erhebliche Rückbildung.	+
40	akute Erkrankung, zuerst als Pneumonie aufgefasst! Rtg. nach 12 Mon. o. B.	+
7	während des Heilstättenaufenthalts Pleuritis. Pneumothorax wegen Tuberkelbazillen im Sputum. Beträchtliche Rückbildung.	—
	vollständige Rückbildung.	+
29	18 Mon. später Rtg. o. B.	—
37	6 ½ Mon. später streifen- und fleckförmige Parenchymverschattung in I 2 links. Bei Rtg. 2 Mon. nach Entdeckung des Primärkomplexes nicht vorhanden gewesen. Beträchtliche Rückbildung.	—
37	lateral in I 2 links einige Streifen. Unverändert.	—
30	1 Mon. nach neg. Rtg. kleinere konfluierende Flecke lat. in I 1—2. Fast vollständige Rückbildung.	—
10	Krankheitsgefühl in der Zeit des Positivwerdens. 8 Mon. später gut abgegrenzte haselnussgrosse Infiltration in I 1 links.	—
26	erbsengrosse fleckförmige Parenchymverschattung an Costa I links. Unverändert.	—
42	neg. Lungenrtg. 5 ½ Mon. nach dem Positivwerden. Nach weiteren 5 Mon. wolkiges Infiltrat in I 1 rechts, welches allmählich kleiner wird. 13 ½ Mon. später streifen- und fleckförmige Verschattung in I 2 rechts.	—
16	neg. Lungenrtg. 15 Mon. nach dem Positivwerden. Nach weiteren 13 Mon. Pleuritis und Lungeninfiltrat lateral in I 1 links und basal. Ein Jahr später Lungenrtg. o. B.	—
13	neg. Lungenrtg. 7 Mon. nach dem Positivwerden. Nach weiteren 3 ½ Mon. Verschattung in Höhe des rechten Hilus, von diesem getrennt. Rückbildung nach 8 Mon.	+

Veränderung kann allerdings auch für ein Frühinfiltrat gehalten werden. Fall 31: Kleine fleckförmige Parenchymveränderung an der ersten Rippe auf der linken Seite, welche 6 ½ Monate nach negativer und 3 ½ Monate nach positiver Tuberkulinreaktion auftrat. Die übrigen drei Fälle haben wir als Fälle von beginnender Lungentuberkulose ohne beobachtete Primärherde betrachtet. Vielleicht kann die Deutung der Fälle 32 und 34 als

Tabelle 7.

Fall	Aussehen des Primärkomplexes
19	2 × 2 cm grosse Verschattung in I 4 unterhalb des mässig vergrösserten rechten Hilus.
20	1 × 1 cm grosse Infiltration lateral in I 4 links. Rechter Hilus schleierartig verschattet.
21	4 × 5 cm grosse kleinfleckige Verschattung in der Höhe des linken Hilus, in den vergrösserten Hilusschatten übergehend.
22	Streifen- und fleckförmige Verdichtung medial im Supraclaviculargebiet und I 1, in den vergrösserten Hilusschatten übergehend.
23	Unter und hinter dem vergrösserten linken Hilus eine fleckförmige, 4 × 4 cm grosse, mit dem vergrösserten Hilusschatten verschmelzende Verschattung.
24	Haselnussgrosses Infiltrat in der rechten Lunge mit stark vergrössertem Hilus.
25	Einige Flecke in der Mitte des linken Lungenfeldes sowie deutlicher Lymphomschatten im linken Hilus.
26	Fleckförmige, 1 × 2 cm grosse Verschattung in I 4, mitten im rechten Lungenfeld gelegen. Hilus vergrössert.
27	Lateral in der Mitte des linken Lungenfeldes schleierartige und streifenförmige Verschattungen sowie verdichteter und deformierter Hilus.

spät zutage tretende Primärherde nicht abgelehnt werden; im Hinblick auf die zeitlichen Verhältnisse neigen wir jedoch nicht zu dieser Auffassung. Fall 32: 1 ½ Jahr nach negativer, 10 ½ Monate nach positiver Tuberkulinreaktion und 5 Monate nach dem letzten negativen Röntgenbefund trat ein wolkiges Infiltrat lateral im ersten Intercostalraum rechts auf; 13 ½ Monate später kam eine streifen- und fleckförmige Verschattung im zweiten rechten Intercostalraum hinzu. Fall 33: 28 Monate nach dem Positivwerden erkrankte Pat. an linksseitiger Pleuritis, und gleichzeitig wurde eine Parenchyminfiltration lateral im ersten Intercostalraum sowie basal auf derselben Seite entdeckt, welche nach und nach verschwand (negativer Röntgenbefund 13 Monate vor dem Erkranken). Fall 34: 19 Monate nach negativer, 10 ½ Monate nach positiver Tuberkulinreaktion und 3 ½ Monate nach negativem Röntgenbefund Verschattung in Höhe des rechten Hilus und von diesem getrennt, welche dann bereits nach 8 Monaten restlos verschwunden war.

Zusammenfassend lässt sich also sagen, dass sich unter diesen 34 Fällen von tuberkulöser Manifestation bei zuvor tuberkulinnegativen Studierenden neben den fünfzehn, bei welchen die Erkrankung mit vollständigen Primärkomplexen oder nur mit Hilusver-

änderungen einsetzte, sowie den beiden mit Infektion in Verbindung mit einer Obduktionsverletzung weitere Fälle finden, die primär-tuberkulöse Veränderungen aufgewiesen haben. Zu diesen gehören die drei Fälle von Erythema nodosum und fünf mit Pleuritiden (6, 7, 10, 11, 12); bei allen acht besteht ein enger Zusammenhang mit dem Positivwerden. Auch vier Fälle mit lediglich Lungenveränderungen (28, 29, 30, 31) dürften in diese Gruppe einzureihen sein. Mithin bleiben fünf Fälle übrig, bei welchen die tuberkulöse Manifestation vermutlich nicht als primäre Tuberkulose aufzufassen ist (8, 9, 32, 33, 34).

Eine Untersuchung der weiteren Entwicklung der Fälle ergibt, dass von 29 Fällen mit Veränderungen der Pleura, des Hilus und Lungenparenchyms nur sieben ein Fortschreiten des Prozesses erkennen liessen. Dasselbe bestand bei zwei von diesen sieben Fällen in der Entwicklung einer Pleuritis (7, 21), bei den übrigen fünf im Auftreten von Parenchymveränderungen verschiedenen Charakters. Letztere hatten in einem Fall das Aussehen einer grossfleckigen Parenchymverschattung in der Höhe des rechten Hilus (19), in einem anderen, wo man früher ein Infiltrat konstatiert hatte, trat dann an einer anderen Stelle eine streifen- und fleckförmige Verschattung auf (32). Das bei Fall 32 beobachtete Infiltrat kann wegen des späten Auftretens nach dem Positivwerden wahrscheinlich nicht der Primärherd sein. Bei den drei restlichen Fällen sowie bei dem oben erwähnten Fall 19 hatte vor dem Fortschreiten ein vollständiger Primärkomplex oder eine Pleuritis bestanden. Die Verbreitung des Prozesses machte sich bei diesen drei letztgenannten Fällen (10, 21, 27) durch kleinere, unscharf begrenzte Flecke bemerkbar, deren Aussehen und Lokalisation mit den von Malmros und Hedvall beschriebenen Initialherden übereinstimmte, welche nach Ansicht dieser Autoren den Beginn und Ursprung der eigentlichen Lungentuberkulose darstellen sollen. In zwei Fällen stellten sich besagte Veränderungen etwa 1 Jahr nach negativer Tuberkulinreaktion und 6—9 Monate nach Feststellung des Primärkomplexes ein. Bei diesen Fällen ist man also berechtigt, die Veränderungen nach Malmros und Hedvall als subprimäre Initialherde zu bezeichnen. In dem dritten Falle beträgt das Intervall zwischen der Primärmanifestation und dem Auftreten der neuen Parenchymveränderungen wenigstens 21 und höchstens 24 Monate (10).

Tabelle 8.

Diagnose	Vollständige Rückbildung	Teilweise Rückbildung	Stillstand d. Prozesses	Fort-schreiten d. Prozesses	Sa.
Pleuritis	5	—	—	2	7
Hiluslymphom	5	1	—	—	6
Primärkomplex	3	1	1	4	9
Veränderungen nur im Lungenparenchym	2	1	3	1	7
Sa.	15	3	4	7	29

Bei den übrigen 22 von den obenerwähnten 29 Fällen ist der Prozess bei vier (20, 28, 30, 31) unverändert geblieben. In drei Fällen (18, 22, 29) fand eine erhebliche partielle Rückbildung statt. Bei den fünfzehn restlichen Fällen war der Rückgang vollständig (s. Tab. 8).

Erörterung.

Die Zahl der frisch Positiven, die von demonstrierbaren tuberkulösen Manifestationen betroffen wurden, ist im vorliegenden Material auffallend klein: nur 34 von 251 oder 14 v. H. Andere skandinavische Untersucher geben beträchtlich höhere Zahlen an, und durch diese älteren Ermittlungen hat sich die Anschauung eingebürgert, dass erstens die tuberkulöse Primärinfektion bei jungen Erwachsenen in sehr grossem Umfang mit tuberkulöser Manifestation einhergeht, sowie zweitens dass diese Manifestation in vielen Fällen eine — entweder unmittelbar oder jedenfalls nach einer relativ kurzen Latenzzeit — schlechte Prognose habe. Was den letzten Punkt betrifft, so hat bekanntlich Heimbeck die Ansicht verfochten, eine nach der Primärinfektion entstehende Lungentuberkulose gehe direkt vom Primärherd aus. Obwohl dies ohne Zweifel in seltenen Fällen zutrifft, so ist es doch als von späteren Untersuchern, z. B. Malmros und Hedvall, bewiesen zu erachten, dass sich eine in verhältnismässig engem zeitlichem Zusammenhang mit der Primärinfektion auftretende Lungentuberkulose in den allermeisten Fällen nicht direkt aus dem primären Fokus entwickelt, sondern mit frischen Herden an anderer Stelle in

Tabelle 9.

Spalte Nr.	Tuberkulin- negative mit Beobach- tungszeit	Beobach- tungsjahre als Negative		Davon frisch Positive		Frisch Positive pro 100 Beobach- tungsjahre	
		Min.	Max.	Anzahl	% der Neg.	Max.	Min.
		II	III	IV	V	VI	VII
Mediziner	116	126	165	62	53	49	38
Übrige Studierende	611	788	922	189	31	24	20
Sämtliche	727	914	1087	251	35	27	23

den Lungen einsetzt. Bei der Beurteilung der Frage der Häufigkeit tuberkulöser Manifestationen bei frisch Positiven erweist es sich als beachtend, eine aus besonders ansteckungsgefährdeten Individuen bestehende Materialgruppe dem Normalmaterial der nicht einer Ansteckung speziell ausgesetzten Personen gegenüberzustellen (Tab. 9).

Ein Vergleich zwischen Medizinern und übrigen Studierenden lehrt zunächst einmal, dass das Umschlagen von negativer zu positiver Reaktion bei den Medizinern viel häufiger erfolgt ist (53 v. H. gegenüber 31 v. H.). Berücksichtigt man auch die Beobachtungszeit, welche seit der ersten Untersuchung vergangen war, und berechnet man die Anzahl der frisch Positiven pro 100 hierdurch erhaltene Beobachtungsjahre, so findet man ebenfalls ein entschiedenes Überwiegen der Mediziner. Auf diese Weise kommt man zu einem zahlenmässigen Ausdruck für das grössere Infektionsrisiko der Mediziner.

Unser Material gewährt tatsächlich die Möglichkeit, einen statistisch gesicherten Beweis für die grössere Ansteckungsgefährdung der Mediziner zu erbringen, unter Berücksichtigung der Zeit, welche zwischen der ersten negativen Probe und dem wirklichen Zeitpunkt des Eintretens der Allergie vergangen ist. Dieser Zeitpunkt lässt sich ja nur ausnahmsweise feststellen (vgl. S. 66), und aus diesem Grunde kann auch die Anzahl der »Beobachtungsjahre als Negative« (Tab. 9) nicht exakt berechnet werden. Man erhält aus der Zeit von der ersten bis zur letzten negativen Probe einen Minimalwert und aus der Zeit von der ersten negativen bis zur ersten positiven einen Maximalwert; zwischen diesen muss der

wirkliche Wert liegen. Durch die auf diese Weise ermittelten Minimal- und Maximalwerte für Beobachtungsjahre (Spalte II—III, Tab. 9) gelangt man zu den entsprechenden Maximal- und Minimalwerten für frisch Positive pro 100 Beobachtungsjahre (Spalte VI—VII, Tab. 9). Das letztere Minimum der Mediziner, 38, ist mit dem mittleren Fehler 3.8 behaftet, während dieser für den Maximalwert, 24, der übrigen Studierenden 1.5 beträgt. Für den mittleren Fehler der Differenz ergibt sich: $\epsilon_{\text{Diff}} = \pm 4.1$. Die Differenz ist also grösser als ihr dreifacher mittlerer Fehler.

Ein anderer Weg, das grössere Infektionsrisiko der Mediziner ersichtlich zu machen, besteht darin, dass man mittels einmaliger Untersuchungen an einem grösseren Material die Tuberkulinpositivität in verschiedenen Altersstufen bestimmt und hierdurch Positivitätskurven für Tuberkulosegefährdete und nicht Gefährdete erhält. Dieses Verfahren ist von uns in einer vorangehenden Arbeit angewendet worden, und wir fanden dabei in der Kurve der Mediziner ein steiles Ansteigen ungefähr zur Zeit des Beginns der klinischen Studien (was mit den Beobachtungen von Lindau und Hedvall hinsichtlich der Ansteckungsgefahr bei Obduktionen in gutem Einklang steht). Eine dritte Methode ist die Berechnung der Häufigkeit des Erkrankens an Tuberkulose bei den zu vergleichenden Gruppen. Da unser Material indessen sowohl mit Tuberkulinproben als auch mit Röntgenaufnahmen laufend kontrolliert wurde, ist es geeignet, über die reine Feststellung einer höheren Tuberkulosemorbidity bei Medizinern hinaus recht interessante Aufschlüsse zu liefern. In Tab. 10 findet man die Anzahl der Fälle mit sichtbaren intrathorakalen tuberkulösen Erscheinun-

Tabelle 10.

	Fälle von intrathoraka- ler Primär- manifestation bei frisch Positiven	In Prozent der Negati- ven nach Tab. 9	Pro 100 Beob- achtungsjahre nach Tab. 9 (Grenzwerte)	In Prozent der frisch Positiven
Spalte Nr.	I	II	III	IV
Mediziner	12	10	7—10	19
Übrige Studierende	12	2	1—2	6
Sämtliche	24	3	2—3	10

gen vom primären Typus, einschliesslich der Pleuritiden des Primärstadiums. Es sei ausdrücklich betont, dass Tab. 10 keine Fälle mit ausschliesslich postprimären Veränderungen enthält. Von unseren 34 Fällen wurden mithin nur 24 in die Tabelle aufgenommen, sämtlich vom Primärtypus. Wie zu erwarten ist, ergibt sich, dass die Zahl derartiger Veränderungen, an Hand der Anzahl Negativer berechnet, für die Mediziner höher ist als für die übrigen Studierenden (10 v. H. gegenüber 2 v. H.). Dies ist eine natürliche Folge des grösseren Infektionsrisikos. Mehr Beachtung verdient der Umstand, dass die Häufigkeit der betreffenden Erscheinungen auch bei Berechnung an der Anzahl derjenigen, welche frisch tuberkulinpositiv geworden sind, für die gefährdete Gruppe wesentlich grösser ist als für die nicht gefährdete (19 v. H. bzw. 6 v. H.¹), m. a. W., die frisch Infizierten, welche einer besonders grossen Ansteckungsgefahr ausgesetzt gewesen waren, bekommen häufiger Primärveränderungen als andere frisch Infizierte. Die Sachlage lässt sich auch so ausdrücken, dass sich die Erstinfektion bei nicht so starkem Ansteckungsrisiko ausgesetzten Individuen relativ öfter nur in einer positiven Tuberkulinreaktion äussert. Dies muss bedeuten, dass es nicht lediglich von endogenen Faktoren abhängt, ob eine Primärinfektion eine sichtbare intrathorakale Manifestation auslöst, sondern dass hierbei auch die Art der Infektion, die Menge oder Virulenz der eindringenden Keime, eine Rolle spielen muss. Unsere Resultate decken sich mit den Folgerungen von Holm, wenn er sagt, dass die Auswirkung des Gefährdungsmoments nicht nur darin besteht, dass eine grössere Anzahl infiziert wird, sondern auch darin, dass diese Angesteckten in einem höheren Prozentsatz röntgenologisch nachweisbare Lungenveränderungen bekommen. Eine Mitteilung von Isager deutet in dieselbe Richtung hinsichtlich der Altersgruppen der Schuljahre. Die Ergebnisse stehen aber im Widerspruch zu der verschiedentlich geäusserten Ansicht, weder der Menge noch der Virulenz der Erreger komme Bedeutung für die

¹ Der mittlere Fehler ist bei der Prozentzahl der Mediziner 5, bei der für die übrigen Studierenden 1,7, $\epsilon_{\text{Diff}} = \pm 5.3$. Die Differenz ist also das Zweieinhalbfache, nicht aber das Dreifache des mittleren Fehlers. Das Verhältnis ist daher als statistisch wahrscheinlich, nicht als sicher, zu erachten. — Legen wir, um grössere Zahlen zu erhalten, unser Material mit dem Holmschen (Untersuchungen an Studierenden in Kopenhagen) zusammen, so ergibt sich für Mediziner 16 ± 2.5 v. H., für übrige Studierende 7 ± 1.6 v. H., Differenz = 9 ± 3 v. H. Der Wert wird mit allem Vorbehalt in bezug auf Materialunterschiede angeführt.

Entstehung von Lungenveränderungen zu. So sagt Bruno Lange, »dass Unterschiede in der Infektionsdosis, soweit sie überhaupt vorhanden, nur äusserst gering sind und auch in kurzen Zwischenräumen oft aufeinanderfolgende Infektionen praktisch keine Rolle spielen können«. Lange gibt zwar zu, dass die Virulenz eine Rolle spielen kann, fährt aber fort: »Die vorgetragene Anschauung der geringen Bedeutung von Schwankungen der Infektionsdosis führt notwendig zu einer weiteren recht wichtigen Schlussfolgerung: wenn es nicht die Infektionsdosis ist, die den Verlauf der Primärinfektion entscheidend beeinflusst — und auch nicht die Virulenz der Bazillen —, können die immer wieder zu beobachtenden auffallenden Verlaufsverschiedenheiten der Tuberkulose im Anschluss an die Erstinfektion nur in erheblichen Verschiedenheiten der individuellen natürlichen Widerstandsfähigkeit begründet sein. Diese natürliche (unspezifische) Resistenz ist in ihren mannigfaltigen Abstufungen bereits bei Beginn der Infektion vorhanden und wird nicht wie die Immunität erst durch sie erworben«. Wir haben indessen keine Anhaltspunkte für die Annahme, dass die natürliche Widerstandsfähigkeit bei den Medizinnern von vornherein geringer wäre als bei den übrigen Studierenden. Es sei nochmals betont, dass wir uns hier nur mit der Entstehung demonstrierbarer Primärmanifestationen bei den untersuchten Gruppen beschäftigt haben.

Die niedrigeren Morbiditätszahlen bei Primärinfektionen, welche wir in unserem Material gegenüber dem anderer skandinavischer Untersucher gefunden haben, werden durch die vorstehenden Ausführungen zum Teil erklärt. Die höheren Zahlen von Heimbeck sind dementsprechend darauf zurückzuführen, dass das grundlegende Material dieses Autors aus in einer Tuberkuloseabteilung angestellten Pflegerinnen bestand. Auch das Kristensonsche Material bestand aus Krankenpflegerinnen. Bei einem gemischten Material wie dem von Malmros und Hedvall — zu diesen gehört auch das unsrige — ist bei einem Vergleich das Verhältnis zu berücksichtigen, in dem gefährdete Gruppen im Material vertreten sind. Unser Gesamtmaterial von rund 6600 Personen enthält etwa 15 v. H. Mediziner, das von Malmros und Hedvall (rund 3300 Untersuchte) ungefähr 32 v. H. Mediziner und Krankenpflegerinnen.

Es ist bei der Besprechung einschlägiger Arbeiten oft auf die Notwendigkeit hingewiesen worden, primäre und postprimäre

tuberkulöse Manifestationen sorgfältig auseinanderzuhalten. Sonst ergeben sich irreführende Schlussfolgerungen bezüglich der wirklichen Lungentuberkulosefrequenz bei frisch Positiven. Wir haben im vorstehenden unsere Fälle mit Rücksicht eben auf diesen Gesichtspunkt eingehend analysiert und bei unseren Schlussfolgerungen diesen wichtigen Unterschied beachtet. Es zeigte sich, dass pulmonale Primäraffekte in Form von vollständigen Primärkomplexen, Hiluslymphomen und Primärherden ohne Beteiligung von Lymphdrüsen nur bei 7.6 v. H. der 251 frisch Positiven vorkamen. Was die Prognose der Erstaffektionen betrifft, so ist diese in unserem Material gut. In keinem Fall wurde mit Sicherheit beobachtet, dass eine beginnende Phthise direkt aus einem Primärherd entstand, sondern dieser liess in der Mehrzahl der Fälle eine mehr oder minder vollständige Rückbildung erkennen. Wo sich progrediente Veränderungen entwickelten, gingen diese von neuen Herden aus, welche in etlichen Fällen mit den von Malmros und Hedvall beschriebenen Initialherden übereinstimmten.

Es ist indessen bemerkenswert, dass sich unter den 34 Fällen mit tuberkulösen Manifestationen nur 7 Fälle mit postprimären Parenchymveränderungen (10, 19, 21, 27, 32, 33, 34) finden, obwohl die durchschnittliche Beobachtungszeit nach dem Positivwerden über 2 $\frac{1}{2}$ Jahre beträgt. Bei keinem dieser Fälle hat sich eine kaveröse Phthise entwickelt. Malmros und Hedvall fanden unter 151 frisch Positiven mit insgesamt 47 Fällen von tuberkulösen Manifestationen nicht weniger als 19 Fälle von postprimären Parenchymveränderungen, wobei die Beobachtungszeit nach dem Positivwerden für die 47 Fälle ebenfalls im Durchschnitt etwa 2 $\frac{1}{2}$ Jahre zu betragen scheint. Unsere Untersuchung vermittelt also nicht einen ebenso markanten Eindruck von der Gefahr, dass sich im Laufe der nächsten Jahre nach einer Primärinfektion im Erwachsenenalter postprimäre Parenchymveränderungen entwickeln. Ein Fingerzeig darüber, dass Menge oder Virulenz der Infektion nicht nur, wie wir oben gezeigt hatten, für das Zustandekommen sichtbarer Primärmanifestationen, sondern auch für postprimäre Bedeutung besitzen, liegt darin, dass sich unter den 19 Fällen von Malmros und Hedvall nicht weniger als 17 Mediziner oder Krankenpflegerinnen befanden. Auf die Frage der Rolle des Gefährdungsfaktors bei einer beginnenden wirklichen Lungentuberkulose wollen wir in einer folgenden Arbeit zurückkommen.

Zusammenfassung.

In einem Material von 6629 Stockholmer Studenten und Studentinnen reagierten 935 oder rund 14 v. H. bei Intrakutanprobe nach Mantoux mit 1 mg negativ. Bei diesen wurden im Anschluss an die Untersuchung Röntgenbilder aufgenommen, und 727 wurden mit erneuten, in kurzen Zwischenräumen aufeinanderfolgenden Tuberkulinproben laufend kontrolliert. Unter den Tuberkulinnegativen waren Frauen und Personen ohne familiäre Belastung stärker vertreten als im Gesamtmaterial. Die Männer und die Individuen mit familiärer Belastung waren m. a. W. in grösserem Umfang in jüngeren Jahren mit Tuberkulose infiziert worden.

Von den 727 Negativen wurden 251 tuberkulinpositiv und mit erneuten Röntgenaufnahmen kontrolliert. Die latenten Primärinfektionen zeigten in zahlreichen Fällen eine schwache oder mässige Allergie. Die frisch Infizierten, welche gesund blieben, wiesen auch durchschnittlich einen niedrigeren Grad von Allergie auf als gesunde, röntgennegative, schon bei der ersten Untersuchung positive Personen desselben Alters. Es war ein grosser Vorteil, dass für alle frisch Angesteckten zum Vergleich eine negative Röntgenaufnahme aus der Zeit vorlag, in der der Untersuchte noch tuberkulinnegativ gewesen war.

Von den 34 tuberkulösen Manifestationen, welche bei den 251 frisch Positiven auftraten, waren 29 von Primärtypus (3mal Erythema nodosum bei Frauen, 2mal Lymphdrüsentuberkulose im Anschluss an eine Obduktionsverletzung, 5mal Pleuritis, 6mal Hiluslymphom, 9mal vollständiger Primärkomplex und 4mal Lungenveränderung).

Für das grössere Infektionsrisiko der Mediziner konnte ein statistisch gesicherter Beweis erbracht werden. Dasselbe äusserte sich darin, dass Mediziner in grösserer Zahl positiv wurden — auch bei Berücksichtigung der Beobachtungszeit. Überdies war bemerkenswert, dass die Hälfte der intrathorakalen Primärerrscheinungen Mediziner betrafen, also wesentlich mehr, als es der relativen Anzahl der Mediziner unter den frisch Positiven entsprechen würde. M. a. W., die frisch Infizierten, welche einer besonders grossen Ansteckungsgefahr ausgesetzt gewesen waren, bekommen der Wahrscheinlichkeit nach häufiger Primärveränderungen als andere frisch Infizierte. Dies lässt sich auch so ausdrücken, dass

sich die Erstinfektion bei nicht so grossem Ansteckungsrisiko ausgesetzten Individuen relativ öfter nur in einer positiven Tuberkulinreaktion äussert. Hierdurch wird wahrscheinlich, dass die Art der Infektion, die Menge oder Virulenz der eindringenden Erreger eine Rolle spielt. Die Übereinstimmung mit den Ergebnissen der Holmschen Untersuchungen und der Widerspruch zu der Anschauung von Lange werden erörtert.

Ein pulmonaler Primäraffekt in Form eines vollständigen Primärkomplexes, eines Hiluslymphoms oder eines alleinigen Primärherds kam nur bei 19 (7.6 v. H.) der frisch positiven Fälle vor. Die Lungenkomponente des Primärkomplexes hatte ein sehr wechselndes Aussehen. In zwei Fällen war der Primärkomplex anfangs als Bronchopneumonie aufgefasst worden. Die Prognose des Primäraffekts war gut. In keinem Fall wurde mit Sicherheit festgestellt, dass eine beginnende Phthise direkt aus dem Primärherd entstand, sondern dieser liess in der Mehrzahl der Fälle eine mehr oder minder vollständige Rückbildung erkennen.

Bei einer Anzahl von den 29 Fällen mit Veränderungen der Pleura, des Hilus oder Lungenparenchyms traten später neue Erscheinungen auf, in zwei Fällen in Form einer Pleuritis. In drei Fällen machte sich das Fortschreiten der Erkrankung durch kleinere, unscharf begrenzte, im oberen Teil der Lunge gelegene Flecke bemerkbar, im Einklang mit den von Malmros und Hedvall beschriebenen Initialherden. Bei 14 von den 34 Fällen wurde Heilstätten- oder Krankenhausbehandlung als indiziert erachtet.

Die Verfasser haben primäre und postprimäre Krankheitszustände streng auseinandergehalten. Postprimäre Parenchymherde wurden bei insgesamt 7 Fällen (2,8 v. H.) von den frisch Infizierten während der Beobachtungszeit festgestellt, was bedeutet, dass unsere Untersuchung nicht einen ebenso markanten Eindruck des Risikos vermittelt, im Laufe der nächsten Jahre nach einer Primärinfektion im Erwachsenenalter postprimäre Veränderungen zu bekommen, wie andere Ermittlungen der letzten Jahre.

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Ferngeräusch (Mühlengeräusch) bei Spontanpneumothorax.

Von

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(Bei der Redaktion am 26. Mai 1943 eingegangen).

Mit der Herzaktion synchrone, in einem Abstand von mehreren Metern hörbare Geräusche dürften zu den Seltenheiten gehören; der Bericht über einen Fall mit derartigen Geräuschen bei Spontanpneumothorax, der u. a. phonokardiographisch untersucht wurde, erscheint daher gerechtfertigt.

Corvisart erwähnt in seiner Arbeit über Herzkrankheiten vom Jahre 1811, dass den französischen Klinikern schon damals durch die Herztätigkeit bewirkte Geräusche von solcher Stärke bekannt waren, dass man sie in einer gewissen Entfernung vom Patienten hören konnte. Laennec gab an, dass diese »Ferngeräusche« selten wären. Er selbst hatte sie nur einige Male im Abstand von ca. $\frac{1}{2}$ Meter gehört. In einem Fall war das Geräusch zuvor noch im Nebenzimmer hörbar gewesen. L. erklärte diese Geräusche damit, dass ein Luft-Flüssigkeitsgemisch im Perikard von der Herzaktion in Bewegung versetzt wird. Andral, welcher ebenfalls einen Fall mit Ferngeräusch beobachtet hatte, hielt diese Theorie für wahrscheinlich. Bricheateau untersuchte 1844 einen Fall von auf traumatischer Grundlage entstandenem Pyopneumoperikard mit einem Geräusch, welches er mit den regelmässigen klatschenden Lauten verglich, die zustande kommen, wenn die Schaufeln eines Mühlrads die Wasseroberfläche treffen.

Morel-Lavallé, dem dasselbe Bild vorschwebte, führte im Jahre 1864 die Bezeichnung »bruit de moulin« oder »bruit de roue hydraulique« ein. Er beschrieb vier Fälle mit diesem Geräusch, welches in sämtlichen Fällen in der Ferne hörbar und im Anschluss an heftige Kontusionen des Brustkorbs aufgetreten war. Bei den drei Fällen, welche obduziert wurden, handelte es sich um eine Herzbeutelruptur, und der Autor war der Ansicht, die Voraussetzungen für das Zustandekommen derartiger Geräusche wären das gleichzeitige Vorhandensein einer Perikard- und Pleuraruptur sowie ein Gemisch von Luft und Flüssigkeit in der Perikard-Pleurahöhle. Beau veröffentlichte 1840 einen Fall mit Ferngeräusch nach einem Messerstich, der den rechten Vorhof verletzt und einen rechtsseitigen Pneumothorax bewirkt hatte.

Im deutschen Schrifttum ist das betreffende Geräusch »Wasserrad« oder »Mühlengeräusch« genannt und als klatschender oder plätschernder Laut, manchmal mit einem Einschlag von Metallklang und meist von fern hörbar sowie mit wechselndem Einsatz in der Systole gekennzeichnet worden. Als Mühlengeräusch beschrieb Reynier die von ihm bei sechs Fällen gehörten Herzgeräusche. Bei einem von diesen bestand eine Perikard- und rechtsseitige Pleuraruptur mit Hämopneumothorax, bei zweien handelte es sich um Verletzungen der linken Brustseite, bei zwei weiteren um linksseitige Rippenbrüche und Hautemphysem; bei einem Fall schliesslich lag ein starker Verdacht auf Rippenbruch sowie ausserdem eine Aufhebung der Herzdämpfung vor. Bei keinem Fall kam ein Ferngeräusch vor. R. versuchte das Phänomen damit zu erklären, dass ein Gemisch von Luft und Blut im Mediastinum zwischen Brustbein und Herzbeutel oder in der Perikardialhöhle beim Schlagen des Herzens in Bewegung versetzt wird. Dieser Ansicht schloss sich Specht an, der einen Fall mit systolischem, im Abstand von einem Meter hörbarem Geräusch nach stumpfem Trauma des Brustkorbes beobachtet hatte. Bei diesem Fall handelte es sich um einen linksseitigen Pneumothorax, dem der Autor nicht die Schuld an der Entstehung des Geräusches gibt. Morris hat über einen ähnlichen Fall mit Pneumothorax auf der linken Seite und einem systolischen Geräusch berichtet, das man im ganzen Zimmer hören konnte. Das Geräusch war in linker Seitenlage verstärkt und vier Tage lang hörbar. Auch Hörnicke veröffentlichte einen Fall mit derselben Genese, aber mit tödlichem Ausgang. Die

Obduktion ergab einen linksseitigen Hämopneumothorax. Der Autor machte auf die Möglichkeit aufmerksam, dass die Brustkorbwand als Resonanzboden wirken könnte. Im Anschluss an eine Kuhlenkampffsche Plexusanästhesie an der linken Seite trat bei einem von Weil beschriebenen Fall ein Ferngeräusch in der Systole auf. W. vermutete, dass es zu einer Lungen-Pleuraverletzung und infolgedessen zu einem mediastinalen Emphysem gekommen war.

Eine ganz neue Theorie hat Gundermann zur Debatte gestellt, der bei Tierversuchen mit Luftembolien einmal unabsichtlich bei Luftereinblasung in die V. cava inf. ein Ferngeräusch erhielt. Er wiederholte den Versuch und erzielte ausnahmslos in kürzerem Abstand hörbare Mühlengeräusche; er machte daraufhin geltend, dass diese Geräusche für Luftembolien in der rechten Herzhälfte pathognomonisch wären. Gleichzeitig besprach er einige bis dahin veröffentlichte Fälle mit Ferngeräusch nach Trauma, u. a. den von Specht, den er selbst zu untersuchen in der Lage gewesen war, und kam zu der Schlussfolgerung, dass Bedingungen für derartige Luftembolien vorgelegen hatten. Als zur rechten Herzhälfte führende Gefäße, welche bei Verletzungen des Brustkorbs in Betracht kommen sollen, werden die Interkostal- und hinteren Bronchialvenen angegeben. Wagner bemerkte während der Operation einer retrosternalen Struma Ferngeräusche, welche man im Abstand von 2 Metern hören konnte, und war der Ansicht, dass es sich um einen Luftembolus in der rechten Herzhälfte handelte. Zwei rasch vorübergehende Hemiplegieanfälle nach 2 bzw. 8 Stunden bekräftigten, wie der Autor meinte, die Theorie und beruhten auf Luftembolien, welche das Kapillarsystem der Lungen passiert hatten. Miles hat über einen Fall von Ferngeräusch berichtet, welches nach Luftertritt in die V. axillaris einige Minuten anhielt. Boyé hatte zweimal im Anschluss an Hämoptysen bei sich selbst während etlicher Tage ein Ferngeräusch gehört. Er dachte sich eine Verbindung zwischen Bronchus und Vene in dem affizierten Lungengebiet als Unterlage einer Luftembolie.

Dass ein Ferngeräusch auf Grund eines Luft-Flüssigkeitsgemisches im Herzbeutel zustande kommen kann, geht aus dem Fall von Stahl und Entzian hervor; diese Forscher ersetzten bei tuberkulöser Perikarditis das Exsudat zum Teil durch Luft, und es machte sich da ein kurzes Plätschern bemerkbar, welches im Abstand von zwei Metern hörbar war. Bei der weiteren Behandlung wiederholte

sich das Geräusch nicht. Die Autoren, welche auch einen Fall mit im ganzen Zimmer hörbarem Ferngeräusch nach stumpfem Trauma gesehen hatten, geben an, dass die Geräusche nicht ganz gleichartig waren. Einen Fall mit Pyopneumoperikard infolge eines auf den Herzbeutel übergreifenden Speiseröhrenkarzinoms mit den ersten Herzton verdeckendem Ferngeräusch hat Tütel beschrieben. Mehrere Forscher haben Tierversuche (Luft-Flüssigkeitsinjektionen in das Mediastinum, den Herzbeutel und das Lungengewebe) angestellt, jedoch ohne irgendwelche Ergebnisse von Belang.

Während des vorigen Weltkrieges berichteten englische Chirurgen über einen bisweilen von fern hörbaren metallischen Knacklaut in der Systole (*»pericardial knock«*) bei Fällen mit penetrierenden Brustwunden. In 9 von 500 derartigen Verletzungsfällen hörten Rees und Hughes dieses Geräusch, bei 4 von diesen in kurzem Abstand. Die Autoren versuchen den Laut damit zu erklären, dass eine kleine Luftsäule in einem durch einen Fremdkörper oder Blutgerinnsel verschlossenen Bronchus von den Herzbewegungen in Schwingung versetzt wird. Munden und Maynard Smith haben einige weitere Fälle mit *»pericardial knock«* beschrieben.

Ferngeräusche sind auch beim künstlichen Pneumothorax¹ konstatiert worden. Albert veröffentlichte 1922 einen Fall mit im ganzen Zimmer hörbarem Ferngeräusch, welches sich im Anschluss an die Neuanlegung eines linksseitigen Pnth. eingestellt hatte. Da A. der Ansicht war, dass ein Luftembolus im Herzen die Ursache bildete, wurde die Behandlung abgebrochen; erst über $\frac{1}{2}$ Jahr später wurde ein Pnth. angelegt, und zwar dann ohne Zwischenfälle. Aus dem Jahre 1926 liegt die Schilderung eines Falles von Junker mit ebenso starkem Nebengeräusch vor, dieses Mal im Zusammenhang mit der ersten Nachfüllung nach Neuanlegung auf der linken Seite. Bei diesen beiden Fällen bestand ein kleiner linksseitiger Pnth. sowie Pleuraverwachsungen in der Unterlappengegend und womöglich pleuoperikardiale Adhäsionen. J. erörtert daher die Möglichkeit, dass das Geräusch extrakardial entstanden sein könnte, lehnt aber diese Theorie ab, da kein Exsudat vorhanden war. Wie die Mehrzahl der älteren Autoren stand er nämlich auf dem Standpunkt, dass sich in irgendeinem Hohlraum ein

¹ Verkürzungen im folgenden: Path. (Pneumothorax), k. (künstlicher), sp. (spontaner).

Gemisch von Luft und Flüssigkeit befinden müsse, damit unter dem Einfluss der Herzbewegungen das Mühlengeräusch zustande kommen könne. Bei rechtsseitigem k. Pnth. fand Tamarin in zwei Fällen als Mühlengeräusch bezeichnete, in einer Entfernung von 3—5 Metern hörbare, schnalzende Geräusche. Er vertrat die durch Röntgenbefunde gestützte Anschauung, dass Reibung in pleuro-perikardialen Verwachsungen die Quelle des Lautes darstelle, während die Pleurahöhle die Rolle eines Resonanzbodens spiele. Hirsch und Sauser haben zwei Pnth.-Fälle mit Ferngeräusch beschrieben. Bei dem einen handelte es sich um einen linksseitigen sp. Pnth. mit sehr hohem Überdruck, der durch Bersten einer Kaverne in einem k. Pnth. entstanden war, bei dem anderen um Neuanlegung eines rechtsseitigen Pnth. Im letzteren Falle kam während dreier Tage eine leichte Hemiplegie vor, und die Autoren schliessen sich der Theorie von den Luftembolien an. Edwards und Simpson berichteten 1939 über drei Fälle mit Ferngeräusch, einen mit linksseitigem und zwei mit doppelseitigem k. Pnth. Bei den beiden letzteren Kranken trat das Geräusch an Zeitpunkten auf, welche einen Zusammenhang mit der linksseitigen Pnth.-Behandlung wahrscheinlich machten. Bei einem Fall bestanden Verwachsungen an den Ober- und Unterlappen, bei einem anderen ein Exsudat bis zur vierten Rippe. Eine phonokardiographische Untersuchung des »pericardial knock« bei zwei Patienten mit k. Pnth. haben Barnwell und Greene vorgenommen. Ob Ferngeräusche vorlagen, ist in der Arbeit nicht erwähnt. Die Geräusche trafen mit wechselndem Einsatz in der Systole ein.

Die Fälle, bei welchen ein Ferngeräusch plötzlich, ohne Zusammenhang mit einem Trauma, aufgetreten war, sind im Schrifttum sehr dünn gesät. Im Jahre 1884 veröffentlichte Petersen einen Fall mit im Abstand von 1 Meter hörbarem Ferngeräusch. Pat. hatte am Tage vor dem Auftreten des Geräusches beim Treppensteigen plötzlich einen Schmerz in der linken Brustseite gespürt. Bei der Untersuchung wurde ein mit den Herzschlägen synchrones Geräusch konstatiert, dass sich nur in linker Seitenlage einstellte und von starken Vibrationen der Herzgrube begleitet wurde. Nach einigen Tagen wurden Geräusche entdeckt, welche als perikardiale gedeutet wurden. Ausserdem wurde tympanitischer Perkussionsschall in der Herzgegend festgestellt. Der Autor hielt ein vorderes mediasti-

nales Emphysem infolge Berstens einer Lungenalveole für vorliegend. Er berichtete gleichzeitig über einen von Edlefsen beobachteten Fall (junger Arzt) mit ähnlichen Symptomen, bei dem die Diagnose Lungenemphysem als wahrscheinlich erachtet wurde. Bei dem ersteren Fall verschwand das Ferngeräusch nach 2 Wochen, bei dem letzteren nach ein paar Tagen.

Tamarin hat 1928 einen Fall von linksseitigem sp. Pnth. mit in einer Entfernung von 3—4 Metern hörbarem, metallisch klingendem Geräusch beschrieben, welches im Sitzen am stärksten war; eines Nachts war es so laut, dass es die anderen Patienten im Schlaf störte.

In demselben Jahre veröffentlichte Lister einen ähnlichen Fall, bei dem sich das Geräusch nur in aufrechter Stellung bemerkbar machte und im Abstand von $\frac{1}{2}$ Meter hörbar war. Es setzte am Ende des ersten Tones ein und war von dem zweiten deutlich getrennt. Das Geräusch, welches L. als »pericardial knock» bezeichnete, war nach 3 Wochen verschwunden. Die Röntgenuntersuchung ergab einen linksseitigen Pnth. (ganze Lunge von Luft umgeben) sowie ein kleines Exsudat. Bei Nachuntersuchung nach 6 Wochen war die Pnth.-Höhle nicht mehr sichtbar. Der Autor stellte eine Theorie auf, gemäss welcher das Geräusch infolge eines partiellen Verschlusses der Art. pulmonalis auf Grund einer Verschiebung derselben zustande kommen soll.

Wolfertth und F. Wood berichteten 1930 über einen Fall mit kleinem linksseitigem sp. Pnth., der sich im Anschluss an einen Ringkampf entwickelt hatte. Die Herztöne sollen, bevor der Kranke in Behandlung kam, im ganzen Zimmer hörbar gewesen sein; dies war aber bei der Untersuchung nicht der Fall. Die Herztöne waren da im Liegen kaum hörbar, im Stehen jedoch gut.

Im Jahre 1939 beschrieben Scadding und P. Wood vier Fälle mit als »systolic click» bezeichnetem Geräusch bei linksseitigem sp. Pnth. Bei zweien der Fälle lag ein Ferngeräusch vor, desgleichen bei einem von Sharpey-Schafer anschliessend veröffentlichten Fall. Bei allen fünf Kranken war das Geräusch über der Herzspitze am lautesten, und seine Intensität wechselte erheblich mit den Körperbewegungen und bisweilen auch mit den Atmungsphasen. Es ist in einer Weise geschildert, welche wahrscheinlich macht, dass es mit dem oben erwähnten »pericardial knock» identisch war; wie bei diesem schwankte der Einsatz in der Systole in den einzelnen Fällen. Bei

zweien der Fälle kamen ausserdem schwächere diastolische Geräusche ähnlichen Charakters vor und bei einem pleuroperikardiale Reibegeräusche. Scadding und Wood waren der Ansicht, das Geräusch könne nur bei kleinem, linksseitigem Pnth. auftreten. In einigen Fällen war die Pnth.-Höhle so klein, dass sie sich bei Durchleuchtung nicht entdecken liess. Um einen Beleg für diese Annahme zu erhalten, legten sie bei vier Fällen auf der linken Seite einen kleinen Pnth. mit 25—150 cm³ Luft an. In zwei Fällen liess sich dasselbe Geräusch wie bei sp. Pnth. erzielen, in einem war dasselbe mehrere Meter weit hörbar. Nach weiterer Insufflation verschwanden die Geräusche.

Frost und Bing haben vor kurzem über einen Fall von linksseitigem sp. Pnth. mit einem systolischen, klatschenden oder schnalzenden, im Abstand von 1 Meter hörbaren Nebengeräusch berichtet. Dasselbe bestand noch nach 10 Tagen, obwohl sich da im Röntgenbilde ein Pnth. nicht mehr nachweisen liess. Die Autoren halten daher für wahrscheinlich, dass man mit Hilfe eines derartigen Geräusches einen linksseitigen Pnth. auch bei negativem Röntgenbefund diagnostizieren kann. Ob der Laut noch bei der letztgenannten Untersuchung von fern hörbar war, geht aus der Arbeit nicht hervor. Eine phonokardiographische Untersuchung wurde bei diesem Fall nicht vorgenommen, aber die Autoren veröffentlichten Phonokardiogramme von zwei anderen Fällen mit Ferngeräusch. Der eine betraf eine junge Frau, welche plötzlich unter Schmerzen in der linken Rücken- und Brustseite erkrankt war, bei der sich jedoch trotz eingehender Untersuchungen keine Diagnose stellen liess. Das Geräusch war im Abstand von 3 Metern hörbar und wies im Phonokardiogramm einen sehr wechselnden Einsatz in der Systole auf. Bei dem anderen Fall handelte es sich um eine Schwangere im 8. Monat. Sie war eine von zwei Kranken, bei welchen die Autoren bei k. linksseitigem Pnth. das charakteristische Geräusch gehört hatten. Ihr Phonokardiogramm zeigte neben demselben Befund wie bei dem vorigen Fall noch diastolische Nebengeräusche ähnlichen Charakters. Bei den vier Fällen von Frost und Bing war das Geräusch nur in linker Seitenlage zu hören.

Sämtliche hier erwähnten Fälle mit Ferngeräusch bei diagnostiziertem sp. Pnth. hatten zuvor gesunde junge Männer mit linksseitigem Pnth. betroffen, und die Prognose war in allen Fällen eine gute.

Bei sieben Fällen hatten die Autoren das Ferngeräusch mit dem Vorkommen eines linksseitigen sp. Pnth. in Zusammenhang gebracht.

Cornils veröffentlichte 1885 einen Fall mit metallisch klingendem Ferngeräusch bei linksseitigem sp. Pnth: (Pat. mit vorgeschrittener Lungentuberkulose). Die Obduktion ergab einen partiellen Pnth. mit glatten Wänden, ohne Exsudat. Der Unterlappen war kollabiert, der Oberlappen emphysematös.

Hamman beschrieb 1939 als spontanes mediastinales Emphysem sieben Fälle mit systolischem Geräusch, in drei Fällen von fern hörbar. Das Geräusch machte sich nur in gewissen Lagen bemerkbar und kam bei ein paar Fällen auch in der Diastole vor. Nur bei zwei Fällen waren sichere Zeichen eines mediastinalen Emphysems vorhanden, beide Male ohne Ferngeräusch, und bei zwei anderen Fällen bestand ein linksseitiger sp. Pnth., bei dem einen mit Ferngeräusch. Der Autor geht nicht auf die Möglichkeit ein, dass das Geräusch mit dem sp. Pnth. zusammenhängen könnte. Als Mühlengeräusch bezeichnete Jehn einen in der Systole und Diastole hörbare, knisternden Laut bei einem Fall von Mediastinalemphysem. Scadding und P. Wood, welche in der Lage waren, die betreffenden Geräusche bei Pnth. und mediastinalem Emphysem zu vergleichen, halten dieselben nicht für gleichklingend.

Caravias und Sala haben 1932 über einen Fall von Ferngeräusch bei einer Schwangeren mit Mitralstenose berichtet und eine Reihe von Fällen mit Ferngeräusch bei Herzaffektionen aus dem Schrifttum angeführt.

Warburg veröffentlichte einen Fall mit Ferngeräusch, welches auf einen beweglichen Thrombus in der rechten Kammer zurückgeführt wurde, und erwähnte, dass Hagedorn ein Ferngeräusch bei zwei Fällen konstatiert hat (k. Pnth. mit Exsudat bzw. Thyreotoxikose mit hochgradiger Abmagerung).

Eigene Beobachtung.

In der Medizinischen Klinik des Karolinischen Krankenhauses hatte Verf. Gelegenheit, einen Fall mit Ferngeräusch zu beobachten. Es handelte sich um einen 23jährigen Mann, der im Dezember 1941 die medizinische Poliklinik aufsuchte.

Keine erblichen Krankheitsanlagen bekannt. Pat. arbeitet seit einigen Jahren als Typograph. Ein Arbeitskollege starb vor einem Jahre an Lungentuberkulose, ein anderer wird wegen derselben Krankheit mit Pnith. behandelt. Pat. ist bei der Berufsgruppenuntersuchung in der Stockholmer Städtischen Tuberkuloseberatungsstelle im März 1936 untersucht worden: Röntgenbefund der Lungen negativ; intrakutane Tuberkulinprobe nach Mantoux positiv.

Als Kind hatte Pat. Masern, Varizellen und Keuchhusten. Hat nicht Diphtherie, Chorea, Polyarthrit, Scharlach oder irgendwelche tuberkulöse Manifestationen gehabt. Fühlte sich in den letzten Jahren ganz gesund.

Am 6. XII. 1941 glitt er auf der Strasse aus, konnte aber einen Fall durch eine Gegenbewegung vermeiden. Er fühlte unmittelbar einen heftigen stechenden Schmerz in der linken Brustseite. Das Gehen fiel ihm schwer, er begab sich aber ohne Hilfe nach Hause, lag einige Tage zu Bett und litt 3—4 Tage lang unter einem ständigen drückenden Schmerz in der linken Hälfte des Brustkorbs. Die Beschwerden verschlimmerten sich bei tiefem Einatmen.

Schon am ersten Abend hörte er eigenartige, klopfende, regelmässige Laute, die aus der Herzgegend kamen, und beobachtete, dass diese nur in linker Seitenlage auftraten. Sie waren so stark, dass sie von den Eltern des Kranken im Nebenzimmer gehört wurden, waren aber nicht mit irgendwelchen stärkeren Beschwerden verbunden. Als Pat. nach 4 Tagen die medizinische Poliklinik aufsuchte, waren auch die Schmerzen beim tiefen Einatmen verschwunden. Die eigenartigen Geräusche konnte er indessen in einer gewissen Lage nach Belieben hervorrufen.

Status: Grosser, grazil gebauter Mann ohne Zyanose oder Dyspnoe. Am Rumpf und den Extremitäten verstreute Psoriasisefloreszenzen. Rachen leicht gerötet. Lungen bei Auskultation und Perkussion o. B. *Herz:* *In Rückenlage:* Töne kaum hörbar, Herzdämpfung aufgehoben. Keine Geräusche hörbar. *Im Sitzen:* Töne von normaler Stärke, weiches, systolisches Geräusch, am lautesten im 3. Interkostalraum links. Spitzenstoss nicht palpabel. Kein Frémissement. *In linker Seitenlage* (keine reine Seitenlage, sondern Übergang in Bauchlage; diese Lage nahm Pat. selbst ein, um die Geräusche in der Herzgegend zu demonstrieren): Man hört ohne Stethoskop synchron mit den Herzschlägen im Abstand von 3—4 Metern einen kurzen, fast explosiv-knallenden Laut, der in seinem Klang an einen hohen Xylophonton erinnert. Auf ihn folgen ähnliche, viel schwächere Geräusche in kleinerer Anzahl, welche bei jedem Herzschlag nicht ganz gleichartig erscheinen. Spitzenstoss kräftig und im 5. Interkostalraum gut sichtbar, desgleichen Pulsationen in benachbarten Rippenzwischenräumen. Starkes Frémissement. Geräusche, Vibrationen und der starke Herzspitzenstoss verschwinden bei ziemlich geringfügigen Veränderungen der Lage. Stethoskopisch lässt sich der stärkste Laut am Ort des ersten Tons lokalisieren. Das im Sitzen konstatierte systolische Geräusch ist erheblich verstärkt. Die übrigen, in einer Entfernung von 1—1½ Metern hörbaren Geräusche sind hinsichtlich ihrer Stärke und Lokalisation weniger kon-

stant. Sämtliche Geräusche sind in der Apexregion am deutlichsten hörbar und verändern sich nicht merkbar mit den Atembewegungen oder wenn Pat. den Atem anhält.

Die *Ekg-Untersuchung* an demselben Tage sowohl mit wie ohne Vorkommen von Nebengeräuschen ergab normale Verhältnisse. Herzfrequenz in beiden Fällen etwa 80 Schläge pro Minute. Blutdruck 120/80. SR 4 mm/1 st. Blutwerte normal. Temperatur normal.

Status sonst in jeder Beziehung normal.

11. XII. 1941 *Röntgenuntersuchung*: Das Herz, dessen Pulsationen regelmässig und rhythmisch sind, misst 14 $\frac{1}{2}$ cm der Länge, 10 $\frac{1}{2}$ cm der Breite nach und 10 cm in sagittaler Richtung. Volumen 640 cm³, 350 cm³ pro qm Körperoberfläche entsprechend. Form normal. Länge, Breite und Dichte der Aorta wie gewöhnlich.

Lungen: Zwerchfellbewegungen gleichförmig, Sinus frei. Über der linken Lungenspitze knapp 1 Quersfinger breiter Pnth. Sonst keinerlei pathologische Veränderungen im Bereich der Pleura, des Hilus oder Lungparenchyms sichtbar. Keine Anzeichen von Rippenbrüchen.

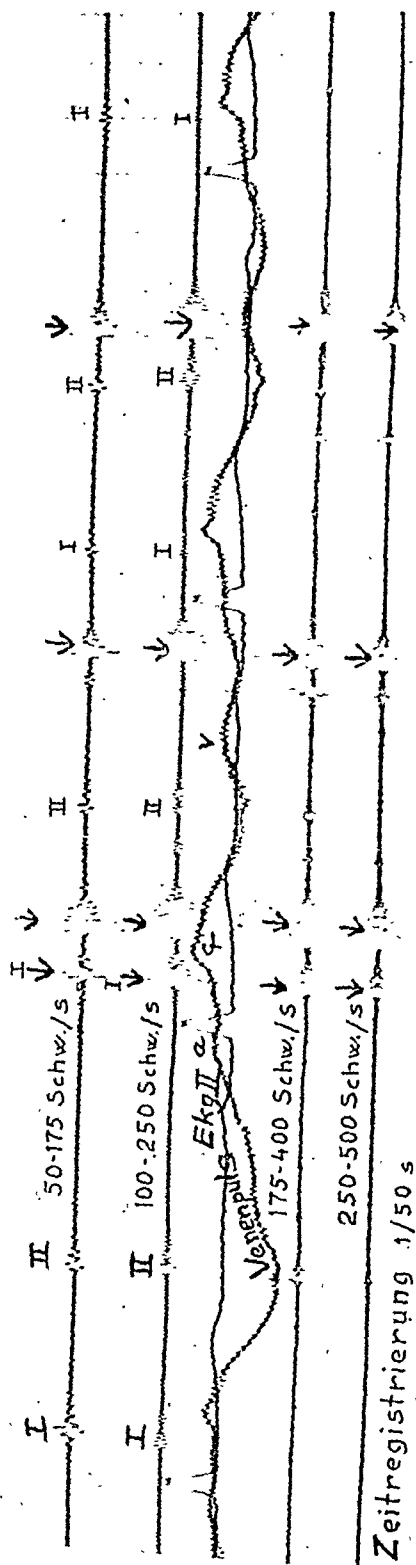
Am 13. XII. wurde eine phonokardiographische Untersuchung in Kronprinzessin Lovisas Vårdanstalt vorgenommen. Pat. hatte da mit gewissen Schwierigkeiten zu kämpfen, wenn er die Geräusche hervorbringen wollte, und meinte, sie wären, wenn dies gelang, etwas schwächer als früher. Laut Untersucher waren dieselben jedoch nach wie vor in der Entfernung durchaus hörbar.

13. XII. 1941 *Phonokardiogramm* (s. Abb. 1): »Töne o. B. Physiologisches systolisches Geräusch (50—250 Schwingungen pro Sekunde). Deutlicher dritter Ton. Anscheinend vollständig unabhängig von der Herzaktion — bei Berücksichtigung von sowohl Ekg wie Phkg und Venenpuls — treten knallende Lautphänomene mit grosser Amplitude und hoher Frequenz auf. Diese Laute kommen völlig unregelmässig, aber man merkt eine gewisse Tendenz zur Salvenbildung (die betreffenden Lautphänomene sind durch Pfeile markiert). *Venenpuls*: Normale Kurve mit a-, c- und v-Wellen. *Ergebnis*: Nichts Pathologisches im Ekg, Phkg oder Venenpuls. Stark knallende Lautphänomene, welche unabhängig von der Herzaktion auftreten. Man dürfte hieraus schliessen können, dass dieselben nicht kardialen Ursprungs sind» (E. Mannheimer).

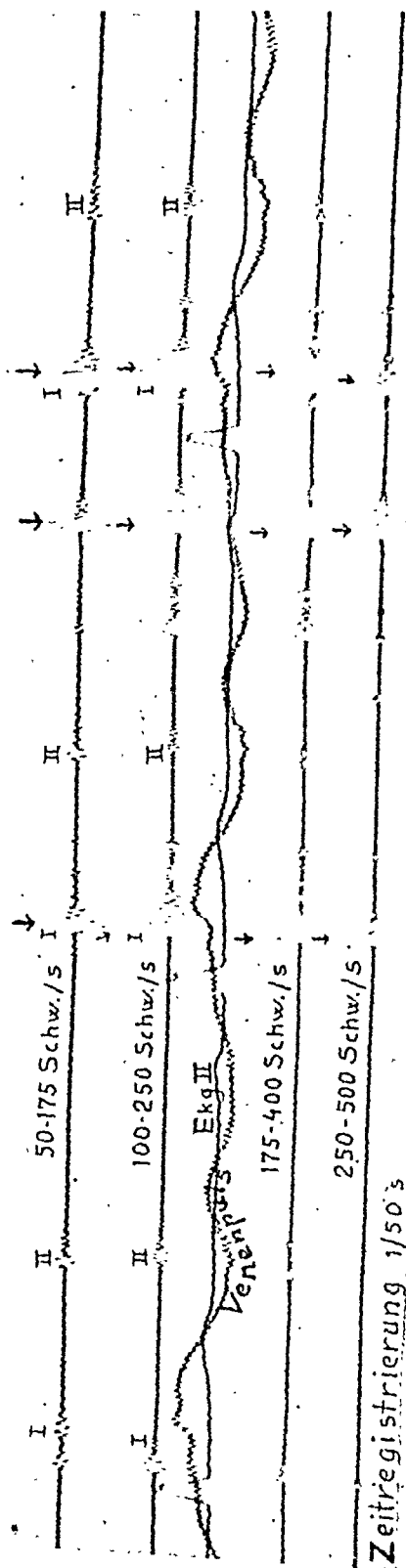
Nach dem 14. XII. hatte Pat. das Geräusch nicht gehört. Bei der Untersuchung am 16. XII. wurde ein weiches systolisches Geräusch wie zuvor konstatiert, ferner bei tiefem Einatmen pleurale Reibegeräusche dicht unter der linken Brustwarze. In Rückenlage waren die Herztöne diesmal gut hörbar. Sonst keine Geräusche.

20. XII. 1941 *Röntgennachuntersuchung*: kein Pnth. Erneute Röntgenuntersuchung am 23. II. 1942 ergab normale Verhältnisse. SR 3 mm/1 st. Auskultationsbefund (Herz und Lungen) normal. Röntgennachuntersuchung ein Jahr nach dem Erkranken: negativer Befund.

Pat. wurde ambulant behandelt (14tägige Schonung zu Hause) und ist nach über einem Jahre noch immer symptomfrei.



a.



b.

Abb. 1. Phonokardiogramm (Frequenzgebiete zwischen 50 und 500 Schwingungen pro Sekunde). Erster Herzton mit I, zweiter mit II bezeichnet. Hochfrequente Lautphänomene mit Pfeilen markiert. Ausserdem sind synchrone Ekg-II- und Venenpulscurve angegeben.

Kommentare und Erörterung.

Es liegt hier also ein Fall mit Ferngeräuschen in der Herzgrube in Verbindung mit einem kleinen linksseitigen Pnth. vor. Der eigenartige Befund mit den starken Geräuschen war überaus eindrucksvoll und verfehlte seine Wirkung auf die Anwesenden nicht. Bei der ersten Untersuchung war es eine Beruhigung, zu wissen, dass die Geräusche nicht im Anschluss an irgendeine therapeutische oder diagnostische Massnahme aufgetreten waren; auch der gute Allgemeinzustand des Kranken liess eine bedrohliche Herzaffektion ausgeschlossen erscheinen, an die man sonst leicht hätte denken können.

Die in Rückenlage aufgehobene Herzdämpfung sowie die kaum hörbaren Herztöne werden dadurch erklärt, dass sich die Luftansammlung in der Pleurahöhle zwischen die vordere Brustwand und das Herz legte.

Eine phonokardiographische Untersuchung des Ferngeräusches beim sp. Pnth. scheint bisher nicht vorgenommen worden zu sein. Das Resultat dieser Untersuchung bei dem vorliegenden Fall war insofern überraschend, als die Geräusche so unregelmässig auftraten. Ich hatte ein starkes, den ersten Ton konstant verdeckendes Nebengeräusch und im übrigen vereinzelte schwächere Laute in der Systole und Diastole erwartet, wie sie an den vorangehenden Tagen einige Male gehört worden waren. Die Lauterscheinungen hatten mithin eine gewisse Veränderung durchgemacht; sie waren auch zwei Tage nach der Phkg-Untersuchung völlig verschwunden. In Abb. 1b fällt jedoch ein Nebenlaut bei zwei aufeinanderfolgenden Herzschlägen ganz mit dem ersten Ton zusammen, und das gleiche findet man ausserdem einmal in Abb. 1a. Sonst treten andere Geräusche — ebenfalls mit hoher Frequenz und grosse Amplitude — anscheinend vollkommen regellos sowohl in der Systole wie in der Diastole auf. Das Phkg bei Rückenlage zeigt nur ein physiologisches systolisches Geräusch und normale Herztöne.

Es liegt auf der Hand, dass die im Schrifttum als »Mühlengeräusch« geschilderten Lautphänomene nicht immer von demselben Charakter gewesen sind. Grössere Einheitlichkeit herrscht hinsichtlich der Beschreibung von Geräuschen beim k. und sp. Pnth. Sie werden als kurze, knackende, schnalzende oder knallende Laute gekennzeichnet. Sicher dürfte sein, dass die Genese der Fern-

geräusche eine wechselnde ist. Gundermann rief dieselben experimentell durch Luftembolien hervor, Tütel, Stahl und Entzian fanden sie bei Pyopneumoperikard, Caravias und Sala u. a. bei Klappenfehlern und mehrere Autoren bei Pnth. In einer Anzahl von Fällen ohne gesicherte Diagnose waren die Umstände solche, dass ein kleinerer k. oder sp. Pnth. vorgelegen haben kann. In etlichen Fällen ist dieser erwähnt, ohne dass die Autoren ihn in Beziehung zu dem Ferngeräusch gebracht haben.

Da sich trotz eingehender Untersuchung keine krankhafte Veränderung am Herzen oder anderen Organen bei den Fällen mit sp. Pnth. nachweisen liess oder wahrscheinlich war, und da eine ganze Anzahl von Fällen mit k. Pnth. veröffentlicht worden sind, ist es offenbar, dass gerade das Vorhandensein eines Pnth. in diesen Fällen die Vorbedingung für das Zustandekommen des Geräusches gebildet hat. Alexander führt zwei mögliche Theorien für die Entstehung dieser Nebengeräusche an. Die eine setzt das Schlagen des Herzens gegen das Zwerchfell über mit Gas gefüllten Bauchorganen voraus, die andere das unmittelbare Anstossen desselben an die Brustwand ohne dazwischenliegendes Lungengewebe. Frost und Bing geben an, bei gleichzeitiger Auskultation und Durchleuchtung festgestellt zu haben, dass das Geräusch nur dann entsteht, wenn das Herz die Brustwand erreicht.

Den Kernpunkt einer anderen Theorie bilden Verwachsungen oder sonstige pleuoperikardiale Veränderungen. Diesen Standpunkt vertreten u. a. Tamarin und Johnston. Der letztere hat während einer Fünfjahrsperiode bei 21 Fällen ohne Pnth. und in den meisten Fällen ohne Anzeichen einer Herzaffektion »systolic click« gefunden. Er versteht darunter Laute, welche dem »pericardial knock« in vielen Beziehungen ähnlich sind, sich aber von diesem u. a. dadurch unterscheiden, dass sie nicht in der Entfernung hörbar sind. Als Beleg für diese Theorie führt er die Sektionsbefunde mit pleuoperikardialen Verwachsungen an, welche Gallavardin bei drei Fällen mit Geräusch in der Systole, unter diesen ein Ferngeräusch, konstatiert hatte.

Es ist wohl wahrscheinlich, dass die Luftansammlung bei Pnth.-Fällen in gewissen Lagen von den Herzbewegungen derart beeinflusst wird, dass sie eine bei jedem Herzschlag wiederholte Auseinandersprengung der beiden Pleurablätter bewirkt und dadurch

einen Laut entstehen lässt (Scadding und P. Wood). Diese Auseinandersetzung kann selbstverständlich örtlich ganz begrenzt sein; womöglich ist erforderlich, dass das betreffende Gebiet der Pleura irgendwie so verändert ist, dass die Adhäsion der Blätter aneinander gesteigert ist. Hierdurch würden die Möglichkeiten für die Entstehung von Vibrationen bei der Trennung der Blätter voneinander und damit für hörbare Laute grösser werden. Bei den sp.-Pnth.-Fällen gibt es ein solches Gebiet, nämlich den Ort der Pleuraläsion. Bei diesem und einigen älteren Fällen sind pleurale Reibegeräusche konstatiert worden. Man kann sich leicht vorstellen, dass die Pleurahöhle unter günstigen Bedingungen einen guten Resonanzboden darstellt, wenn ein Nebengeräusch erst einmal entstanden ist.

Diese Theorie erklärt, weshalb Ferngeräusche nur bei gewissen Körperstellungen vorkommen, die von Fall zu Fall wechseln, und weshalb sie verhältnismässig unbeständig sind.

Verf. gestattet sich, Herrn Dozent E. Mannheimer an dieser Stelle seinen herzlichen Dank für die wertvolle Hilfe auszusprechen, welche die phonokardiographische Untersuchung dargestellt hat.

Zusammenfassung.

Verf. gibt zunächst einen kurzen Überblick des Schrifttums über die präkordialen Nebengeräusche. Diese werden als »pericardial knock«, »systolic click«, »Mühlengeräusch«, »bruit de moulin« und »Distancelyd« (dänisch) bezeichnet und sind in verschiedener Weise erklärt worden. Es folgt dann die Beschreibung eines Falles: 23jähriger Mann mit linksseitigem Spontanpneumothorax und im Abstand von 3—4 Metern hörbarem Geräusch. Das Geräusch trat nur auf, wenn Pat. auf der linken Seite lag. Das Schrifttum enthält sieben Fällen von Spontanpneumothorax — stets auf der linken Seite — mit »Ferngeräusch«, aber keiner derselben ist wie der vorliegende mittels Phonokardiographie untersucht worden.

Summary.

The author reviews the literature of praecordial extra sounds. These are called »pericardial knock», »systolic click», »Mühlengeräusch», »bruit de moulin» and »Distancelyd» (Danish) and have been explained in different ways. He describes a case of a man, 23 years old, with left-sided spontaneous pneumothorax and extra sounds audible at a distance of 3—4 metres. The sounds only appeared, when the patient was lying on his left side. In literature 7 cases of spontaneous pneumothorax — all of which left-sided — with »distance-sounds» have been described, but none of these has — as this case — been studied by means of phonocardiography.

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Der Sauerstoffverbrauch bei hochgradiger Obesitas.

Von

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(Bei der Redaktion am 8. März 1943 eingegangen).

Eine 46jährige, 156 cm lange Frau magerte bei 8monatigem Krankenhausaufenthalt von 170 auf 85 kg ab. Der Fall ist ein kasuistischer Beitrag zur Frage des erhöhten Sauerstoffverbrauchs bei hochgradiger Obesitas und der Hyperthyreose als vermutlicher Ursache dieser Steigerung. Es wird ein Versuch beschrieben, unter Ausnützung des in Tierversuchen festgestellten Synergismus Thyroxin-Dinitrokresol eine etwaige Hyperthyreose objektiv nachzuweisen.

Die Mutter der Patientin starb mit 56 Jahren aus unbekannter Ursache. Die letzten 10 Lebensjahre war sie sehr fettleibig gewesen. Die 9 Geschwister der Patientin und die übrige Verwandtschaft sind nicht ausgesprochen korpulent. Der Mann, Arbeiter, ist mager. 8 gesunde Kinder.

Als Mädchen war die Patientin schlank zu nennen. Sie heiratete mit 21 Jahren. Nach der Geburt des 4. Kindes 10 Jahre später begann sie an Gewicht zuzunehmen. Während der folgenden 10 Jahre, wo sie weitere 4 Geburten und 1 Abort hatte, nahm sie von 86 auf 125 kg zu. Die Menstruationen waren stets und sind noch normal. Seit dem 39. Lebensjahr zunehmende Atemlosigkeit und Herzklopfen bei Anstrengungen, abends waren auch die Beine geschwollen, besonders das rechte. Mit 41 Jahren magerte sie durch Diät und Thyreoidea fast 23 kg ab. Sie setzte jedoch mit den Tabletten aus und hatte ein Jahr später wieder das frühere Gewicht. Die folgenden Jahre noch 2 ähnliche Abmagerungskuren. Bald nach der Heimkehr aber hatte sie ihr Gewicht wieder. Ausserdem nahm die Frau mit

der Zeit immer mehr zu. Mit 45 Jahren wog sie 170 kg. Es fiel ihr jetzt schwer, ohne fremde Hilfe für den Mann und die 8 Kinder den Haushalt zu führen, sie war atemlos und müde, traurig und nervös. Die Beine schwellen an und wurden wund.

Das Aussehen vor und nach der Abmagerungskur geht aus den Abbildungen 1 und 2 hervor. Bei der Aufnahme in die Klinik zeigte die Frau ausgeprägte Myxödemsymptome mit trockener Haut, trockenem Haar, spröden Nägeln und Hartleibigkeit. Ihre Korpulenz ist auch vom myxödematösen Typus, Rumpf und Gliedmassen umfassend. Keine Hypertonie oder Erhöhung der Pulsamplitude (120/80), kein Tremor, in Ruhe normale Pulsfrequenz, bei Glykosebelastung normale Verhältnisse.

In der Klinik bekam die Frau eine Diät von etwa 600 Kalorien pro Tag. Keine Anzeichen von Acidose. Von einer kürzeren Periode in der Mitte der Kur abgesehen, bekam sie täglich eine kleinere Menge Thyreoidea (Schilddrüsentabletten mit 0.4 mg Thyroxin; an einigen Tagen wurde die Dosis auf 0.8 mg erhöht). Ausserdem bekam sie während eines Teils der Kur Dinitrokresol.

Im Verlauf der Kur verschwanden die Myxödemsymptome allmählich so, dass die Haut normale Feuchtigkeit zeigte usw. Doch war das Haar bei der Entlassung aus der Klinik immer noch ziemlich trocken. Besonders interessant ist in diesem Zusammenhang der absolute Sauerstoffverbrauch bzw. Grundumsatz der Frau, berechnet in Prozent des Normalwertes nach den üblichen Tabellen.

Anfangs, vor der Thyreoideabehandlung, entsprach der Sauerstoffverbrauch in Ruhe 3180 Kalorien pro Tag (+ 33 %). Bei etwa 100 kg war der Wert 21700 Kalorien (+ 13 %) und am Ende der Kur 1490 Kalorien (—6 %), welcher letztgenannter Wert aus unserem Laboratorium für leichtes Myxödem spricht. Der respiratorische Quotient ist leider nicht bestimmt worden. Bei sämtlichen Bestimmungen bekam sie dieselbe kalorienarme Abmagerungsdiät.

Der absolute Sauerstoffverbrauch in Ruhe nimmt also während der Abmagerungskur um mehr als die Hälfte ab, trotzdem die Patientin Thyreoidea erhält. Bei Beginn der Kur würde der berechnete Wert des Grundumsatzes für Hyperthyreose, am Ende der Kur für Myxödem sprechen. Bei Beginn der Kur bestanden klinische Myxödemsymptome, die mit der Zeit verschwanden.

Tabelle 1.

Die Einwirkung von Dinitrophenol auf den Grundumsatz von 4 Versuchspersonen vor und nach Thyreoidabehandlung.

Zunächst wurde der normale Grundumsatz der Versuchsperson an verschiedenen Tagen bestimmt, bis konstante Werte erhalten wurden. Dann folgte der eigentliche Versuch, während dessen die Versuchsperson die ganze Zeit nüchtern war. Erst wurden 3 Normalwerte bestimmt. Dann wurden 2 mg Dinitrophenol pro kg Körpergewicht subcutan in 3 %iger Lösung injiziert. 20—30 Minuten nach der Injektion wurde mit der Bestimmung des Sauerstoffverbrauchs in Zehminutenperioden in dichter Folge begonnen. Die Bestimmungen wurden so lange fortgesetzt, bis der Dinitrophenoleffekt abzunehmen begonnen hatte. In der Tabelle wird teils der Wert angegeben, der in der Periode der maximalen Steigerung gefunden wurde (Max.), teils der Mittelwert (Mitt.) für die vorgenannte Periode sowie die unmittelbar vorangehende und die sich anschliessende.

Daran schloss sich die Behandlung mit Schilddrüsentabletten während einer in der Tabelle angegebenen Anzahl von Tagen an; 0,4—0,8 mg Thyroxin pro Tag.

Bei Abschluss der Thyreoidabehandlung wurden erneut an verschiedenen Tagen wiederholte Bestimmungen des Grundumsatzes vorgenommen. Anschliessend wurde der Versuch mit Dinitrophenol nach dem früheren Schema wiederholt. Die Versuchsperson bekam dieselbe absolute Dinitrophenolmenge, weshalb die letzte Dosis im Verhältnis zum Körpergewicht etwas grösser ist.

Vor der Thyreoidabehandlung				Thyreoiden- behandlung Tage	Nach der Thyreoidabehandlung			
Grundumsatz			Gewicht kg		Grundumsatz			Gewicht kg
Kontroll- wert	Nach Dinitro- phenol				Kontroll- wert	Nach Dinitro- phenol		
	Max.	Mitt.				Max.	Mitt.	
+ 2	+22	+20	87.4	14	+36	+56	+51	84.8
+ 7	+26	+25	96.2	28	+44	+66	+61	88.7
+11	+26	+23	114.0	16	+22	+35	+33	109.2
+19	+52	+50	80.1	20	+43	+75	+69	73.3

Short und Johnson (1936) haben etwa 80 Patienten mit einem Übergewicht von 1—135 % studiert. Sie finden, dass der totale Kalorienverbrauch mit zunehmender Obesitas ansteigt. Dies dürfte die Erklärung sein, weshalb diese Patienten, nachdem sie ein konstantes Gewicht erreicht haben, ohne weitere Gewichtszunahme mit der Luxuskonsumtion fortfahren können, die in der Regel als die wesentliche Ursache der Fettleibigkeit angenommen wird.

1928 haben Strang und Evans die Vermutung geäussert, dass viele Patienten mit Fettsucht thyreotoxische Symptome aufweisen. Short und Johnson fanden bei stärkerer Obesitas u. a. höhere Pulsfrequenzen, was sie als ein Hyperthyreosesymptom deuten. Folglich halten sie eine weitere Steigerung des Stoffwechsels durch

Thyreodea o. dgl. bei hochgradiger Obesitas im Anfang der Abmagerungskur für nicht angezeigt. Sie finden die Reduktion der Kalorienzufuhr in der Regel für ausreichend. Thyreodea ist also bis



Abbildung 1. Die Patientin bei 160 kg.

gegen Ende der Abmagerungskur, wenn die Verbrennung abzunehmen begonnen hat, aufzusparen.

S. und J. haben keinen Fall mit einem so bedeutenden Übergewicht wie in dem hier vorliegenden, deshalb auch keinen so grossen Gewichtsunterschied vor und nach der Abmagerung.

Short (1936 und 1941) hat einen Fall von Gewichtsabnahme um 118.4 kg von 180 auf 71 kg im Laufe von 20 Monaten beschrieben, und einen zweiten mit einer Abnahme um 135 kg von 217.5 während 18 Monaten. In den Gewichtsverlust ist dabei auch die exstirpierte überflüssige Bauchhaut eingerechnet, die der abgemagerten Patientin wie eine Schürze herunterhing. In Shorts Fall wie in dem unseren kam die Gewichtsabnahme zeit-



Abbildung 2. Die Patientin bei 86 kg.

weilig zum Stillstand, und zwar infolge von Ödemansammlung, die durch Diuretica behoben wurde.

Die klinischen Myxödemsymptome zur Zeit der hochgradigen Obesitas, die trotz sinkenden Stoffwechsels im Laufe der Abmagerung verschwinden, sprechen mit Bestimmtheit gegen Hyperthyreose als Ursache des hohen Kalorienverbrauchs bei Fettleibigkeit in diesem Falle. Auch liegen keine thyreotoxischen Symptome vor.

Der Fall zeigt somit, dass der Sauerstoffverbrauch bei hochgradiger Fettleibigkeit bedeutend erhöht sein kann, ohne dass ein triftiger Grund vorliegt, Hyperthyreose anzunehmen.

Es wurde folgender Versuch gemacht, eine etwaige Hyperthyreose bei dem Zustand hochgradiger Obesitas der Patientin durch Ausnützung des Synergismus Thyroxin-Dinitrokresol nachzuweisen.

Gewisse Dinitroverbindungen, Dinitrokresol und Dinitrophenol, waren vor einigen Jahren als Abmagerungsmittel sehr im Schwang. Diese Stoffe steigern die Verbrennung schon nach etwa einer halben Stunde oder noch kürzerer Zeit, je nach dem Einverleibungsweg. Die Wirkung einer Einzeldosis nimmt bereits nach 1—2 Stunden stark ab. Im Gegensatz dazu beginnt die Wirkung des Thyroxins erst weit später und bleibt wochenlang bestehen.

Der Verf. zeigte 1935, dass die Einwirkung einer gewissen Menge Dinitrophenol oder Dinitrokresol auf den Sauerstoffverbrauch des Kaninchens vervielfacht werden kann, wenn das Tier mit Thyroxin vorbehandelt wird. Es handelt sich nicht um eine einfache Addition des Effektes der beiden Oxydationskatalysatoren, sondern es liegt ein Synergismus vor. Der Verfasser weist darauf hin, dass dieser Synergismus erwartungsgemäss offenbar auch beim Menschen auftritt: Poole und Haining, 1934, haben einen Todesfall nach mässiger Dinitrophenoldosis eines Patienten, der vorher Schilddrüsentabletten bekommen hatte, mitgeteilt. Der Tod trat in der für Dinitrophenolvergiftung typischen Weise unter äusserst starker Dyspnoe auf.

Unsere Patientin erhielt bei 158 und 91 kg 1 mg Dinitrokresol pro kg Körpergewicht. Die Steigerung des Sauerstoffverbrauchs betrug + 14 % bzw. + 17 %. Da die Dinitrokresolwirkung bei dem höheren Gewicht (und der absolut grösseren Dinitrokresoldosis) nicht grösser ist, kann also kein solcher Grad von Hyperthyreose vorliegen, dass der Dinitrokresoleffekt dadurch verstärkt wird. Der negative Ausfall dieses Versuchs ist indessen nicht beweisend.

Wie aus dem folgenden hervorgeht, bedarf es offenbar einer grösseren Menge eines Dinitropräparats und mit aller Wahrscheinlichkeit einer starken Hyperthyreose, wenn sich der Synergismus geltend machen soll.

Tabelle 1 zeigt, dass bei den üblichen therapeutischen Dosen von Dinitrophenol und Thyreoidea die Bedingungen für einen Synergismus nicht eintreten. Mit grösster Wahrscheinlichkeit kann man nicht ohne allzu grosse Unannehmlichkeiten oder Risiken die fraglichen Oxydationskatalysatoren in solcher Menge verabfolgen, dass Synergismus auftritt. 2 mg Dinitrophenol pro kg subcutan bewirkt eine etwa gleich grosse Steigerung des Sauerstoffverbrauchs bei ein und derselben Person vor und nach Thyreoideabehandlung. — Versuche mit Dinitrokresoltabletten hatten gleichsinnige Ergebnisse.

Ein Unterschied gegenüber den Tierversuchen (Alwall, 1935) liegt darin, dass die Kaninchen während einer kurzen Zeit weit grössere Thyroxindosen bekamen, die einen starken Gewichtsverlust verursachten, und dass eine mehrfach grössere Menge Dinitrophenol verabfolgt wurde.

Der Verfasser hatte gehofft, den Synergismus Thyroxin-Dinitrokresol therapeutisch nutzbar zu machen. Da schwere Hyperthyreosen keinen Katarakt bekommen, könnte man möglicherweise vermuten, dass es die rein chemischen Eigenschaften der Dinitroverbindungen und nicht ihre Wirkung als Oxydationskatalysatoren sind, welche den Star verursachen. Schon von vornherein musste indessen der Vorbehalt gemacht werden, dass auch relativ kleine Dosen Dinitrokresol Katarakt hervorrufen können.

Die in Tabelle 1 angeführten Ergebnisse machen es indessen unwahrscheinlich, dass eine Kombination von Thyreoidea und Dinitrokresol therapeutische Resultate ergeben würde, die über die Addition der Wirkungen beider Stoffe hinausgingen. Es hat sich auch bei therapeutischen Versuchen mit Schilddrüsentabletten + Dinitrokresol nicht als möglich erwiesen, solche Gaben einzuverleiben, dass ein Synergismus von praktischer Bedeutung hervorgetreten wäre. Der Verfasser hat in einem Falle auch bei derartiger Kombinationstherapie einen leichten Katarakt gesehen. Es schien daher nicht gerechtfertigt, diese Behandlungsform noch weiter zu erproben.

Die wesentliche Therapie bei Obesitas muss die Reduktion der Kalorienzufuhr sein, im Bedarfsfalle durch Thyreoidea und evtl. den Appetit herabsetzende Mittel wie Bazedrin unterstützt.

Zusammenfassung.

Eine 46jährige, 156 cm lange Frau magerte während eines 8monatigen Klinikaufenthaltes von 170 auf 85 kg ab. Der absolute Sauerstoffverbrauch in Ruhe nahm während der Abmagerung um mehr als die Hälfte ab, trotzdem die Patientin täglich eine kleinere Menge Thyreoidea erhielt. Nach den üblichen Normen berechnet, war der Grundumsatz bei Beginn der Abmagerungskur +33 %, bei Abschluss derselben -9 %. Zu Anfang bestand klinisch einwandfrei ein Myxödem; die Myxödemsymptome verschwanden allmählich.

In der Literatur findet sich die Angabe, thyreotoxische Symptome seien bei Obesitas häufig und bedingten u. a. den erhöhten Stoffwechsel.

Der vorliegende Fall zeigt, dass der Sauerstoffverbrauch bei Myxödem mit hochgradiger Fettleibigkeit bedeutend gesteigert sein kann, ohne dass ein triftiger Grund vorliegt, Hyperthyreose anzunehmen.

Einige Versuche über die Möglichkeiten einer Kombinations-therapie Thyreoidea + Dinitrophenol(-kresol) werden besprochen.

Literatur.

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From the Medical Out-patient Clinic of the Rigshospital, Copenhagen.
(Chief: Professor Eggert Møller, M. D.)

Treatment of angina pectoris with diethylamino-ethoxy-2-diphenyl hydrochloride.

By

OSKAR THORDARSON

(Submitted for publication June 21, 1943).

Introduction.

The first report on the employment of diethylamino-ethoxy-2-diphenyl in the treatment of angina pectoris was published in 1939 by Clerc & Sterne (5) who had treated 19 patients suffering from angina pectoris of diverse etiology with the result that 14 improved considerably, the tendency to attacks being reduced in a very marked degree. Of these 19 patients 9 had presented electrocardiographic changes; and of these 9 patients 7 improved, while the condition remained unchanged in 2. Among 8 patients who showed no electrocardiographic changes, the treatment had a favorable effect in 5, no effect in 3. Finally, the treatment had a favorable effect in 2 patients with syphilitic aortitis and insufficiency of the left ventricle, respectively. The longest observation period was one year.

Previously the same authors had worked with a related substance, diethylamino-methyl-2-diphenyl, with good effect on patients with angina pectoris. Thus, Sterne (6) had treated 4 pati-

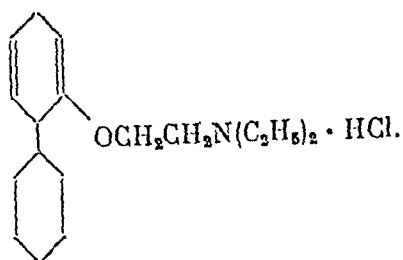
ents with this substance and obtained a favorable effect in all of them; and Clerc, Sterne & Lenoir (4) had treated 25 patients and obtained an excellent effect in 15, some of these patients being symptom-free for up to two years (7). Further, Audier (1) has treated 21 angina pectoris patients with diethylamino-methyl-2-diphenyl, among whom a lasting improvement was obtained in 7, transitory improvement in 6, and no effect whatever in 8. In this patient material the longest observation period was one year. These two substances are said to have the same therapeutic effect. But, while diethylamino-methyl-2-diphenyl was often found to give anorexia, nausea and vomiting, these by-effects were not seen on employment of diethylamino-ethoxy-2-diphenyl. The dosage employed was 5 cg by mouth, 2—3 times daily. In those cases where a therapeutic effect was obtained, it appeared quickly, and this effect also subsided rapidly after discontinuance of this medication.

For the time being, outside the papers cited above, no literature on this subject has been accessible to the writer. The experimental pharmacology of diethylamino-ethoxy-2-diphenyl has been investigated by Bovet, Fourneau, Tréfouel & Strikler (2) and by Tréfouel, Strikler & Bovet (7). From the findings of these authors it is evident that the substance in dogs and guinea-pigs gives dilatation of the coronary circulation and has an antifibrillatory effect. On comparison of the effect of the substance in these experiments with that of theophylline ethylene-diamine and quinidine, it was found that diethylamino-ethoxy-2-diphenyl had not only a stronger but also a more protracted effect. The mode of action of this substance is not known with certainty. Of the two theories advanced — action on the sympathetic nervous system or muscular action — the latter is taken to be the more probable.

Preparation.

In the following an account will be given of the results obtained by employment of diethylamino-ethoxy-2-diphenyl in 22 cases of angina pectoris. The preparation here employed was placed at the disposal of the writer by Løvens kemiske Fabrik, Copenhagen, under the proprietary name «cardifenyli». The drug is manufactured in tablet form, each tablet containing 5 cg.

Cardiferyl is diethylamino-ethoxy-2-diphenyl hydrochloride, the constitutional formula of which is



The substance is colorless, crystalline, soluble in water and alcohol, but only slightly in ether; its melting point is $141-144^{\circ}$. Chloride determination shows a purity of 99.5—100 %. It gives no reaction for metals or trace of foreign acids.

Patient Material.

Altogether 22 patients have been treated with this remedy, 14 men and 8 women, aged from 45 to 71 years, who applied to the Medical Out-patient Clinic of the Rigshospital in the period of June 1942—March 1943. All the patients come from the same social class, belonging to the laboring class. Of these patients 15 have not been treated for the heart lesion before, while the remaining 7 have been treated with nitroglycerine and various purine derivatives for a period of from one month to 11 years. The chief complaint of these patients has been precordial or retrosternal pain, with or without radiation, induced by physical exertion, emotional excitement, cold, meals, and in some cases the pain has set in also when the patient was at rest — for instance, at night. Prior to the treatment with cardiferyl, all the patients have been treated with nitroglycerine, which has had a favorable effect on the acute attack in every instance. The etiological diagnosis is shown in Table 1.

Table 1.

Etiological Diagnosis of Angina Pectoris in the Present Material.

Arteriosclerosis; Arterial hypertension	15
Arterial hypertension	7

Electrocardiography showed pathological changes in 16 patients. On roentgenography, 8 patients presented an increase in the width of the heart (Nos. 2, 3, 4, 10, 11, 12, 16 and 22), whereas in 4 patients the increase in width was limited to the aorta alone (Nos. 1,

Table
Schematic Survey of Clinical Data of

Pl. No.	Record No.	Sex	Age	Height cm	Weight kg	Loss of weight under treatm. kg	Blood pressure		Electrocardiogram
							Before treatment	After treatment	
1	306/42	M.	69	170	75.4	—	180/85	165/85	Left preponderance. Isoel. T ₁ . Extrasystoles.
2	1458/42	F.	68	153	56.6	2	170/100	155/80	Left preponderance. Isoel. T ₂ . Negative T ₃ .
3	253/34	F.	70	158	67.5	—	175/100	155/85	Left preponderance. Isoel. T ₂ . S ₂ large. T ₃ neg.
4	2975/42	M.	51	178	83.1	—	140/95	150/90	Low voltage.
5	1482/35	M.	71	162	66.8	—	170/100	160/90	Left preponderance. T ₁ and T ₂ neg. T ₃ isoel.
6	3256/42	M.	53	176.5	73.1	—	160/90	150/90	Normal.
7	3443/42	M.	62	174	85.1	2	150/100	130/90	Left preponderance. T ₁ neg.
8	3484/42	M.	68	167.5	89	6.7	160/90	130/80	Left preponderance. T ₁ neg.
9	2143/31	M.	47	169	84.9	—	150/100	150/100	Left preponderance. T ₂ and T ₃ neg.
10	1629/42	F.	67	150	52.7	4.7	200/90	210/100	Left preponderance. T ₁ isoel.
11	2162/42	F.	61	152	97.2	7.7	175/100	175/100	Left preponderance. T ₁ isoel.
12	289/43	F.	59	169	72.4	—	180/100	235/100	Left preponderance. T ₁ and T ₃ neg.
13	3217/42	M.	45	167	85.5	1.8	200/100	185/100	T ₁ negative.
14	2924/42	M.	54	156	60.9	—	160/85	135/80	Q ₂ large.

2.

Patients Treated with Cardiferyl.

Cardiferyl			Placebos			Result of cardiferyl therapy	Remarks
Total dose (g)	No. of in days	Effect	Total dose (g)	No. of in days	Effect		
3.15	21	Good	6.6	33	Good	—	
4.10	26	Good	4	20	Good	—	
2.10	14	Good	4.20	28	Good	—	
1.4	7	Good	7.6	38	Good	—	
11.0	55	Good	4.8	24	Good	—	
12.1	54	Good	12.3	41	Good	—	Hb %: Before treatm. 83 After 95
4.2	21	Good	10.4	52	Good	—	
8.0	28	Good	8.2	21	Good	—	
5.2	26	Good	5.2	13	Good	—	
5.55	37	Good	1.0	7	Good	—	Hb %: Before treatm. 80 After 96
1.05	7	Good	1.05	7	Poor	Good?	At the same time, treated for diabetes mellitus.
8.4	21	Good				Good?	Hb %: Before treatm. 75 After 110 Died of coronary thromb.
29.4	83	No				—	
10.8	42	No				—	

Table

Pl. No.	Record No.	Sex	Age	Height cm	Weight kg	Loss of weight under treatm. kg	Blood pressure		Electrocardiogram
							Before treatment	After treatment	
15	2873/42	M.	61	168	79.5	0.8	150/90	135/100	Normal.
16	3710/42	F.	70	151	68.1	1	280/110	220/100	Right bundle branch block (Bayley's Type 3).
17	155/43	M.	58	160.5	67.4	—	145/90	155/90	Left preponderance. T_1 diphasic.
18	3370/43	M.	58	167	71.5	—	150/90	145/100	Left preponderance. Normal.
19	1675/40	F.	52	147	52.3	2	190/80	170/85	Normal.
20	1356/42	M.	55	172	69.5	—	165/90	165/90	Left preponderance. S_2 large. T_1 low.
21	3252/42	M.	55	168	89.8	—	145/90	135/90	Left preponderance. Normal.
22	2321/32	F.	62	165	85.2	5.5	220/120	190/120	Left preponderance. Extrasystoles.

5, 7, 15) (see Table 2). The rest (10 patients) had a normal X-ray picture.

Treatment.

To begin with, a daily dose of $5 \text{ cg} \times 3$ was given. When the desired effect failed to appear, however, the dose was increased so that some of the patients were given $10 \text{ cg} \times 3-4$ daily for several weeks in succession. In those cases where cardifenyl appeared to have a favorable effect, in order to exclude the possibility that this apparent effect was suggestive, the administration of cardifenyl was discontinued without the knowledge of the patients who then were given a placebo in the form of tablets that could not be distinguished from the real drug. All the patients were directed explicitly not to take any other form of medicine as long as the treatment lasted; but this rule could not be carried through con-

2. (Cont.)

Cardiferyl			Placebos			Result of cardiferyl therapy	Remarks
Total dose (g)	No. of in days	Effect	Total dose (g)	No. of in days	Effect		
21.5	32	No				—	
7.7	37	No				—	Hb %: Before treatm. 75 After , 82
6.3	23	No				—	
9.2	21	No				—	
4.1	17	No				—	
2.1	14	No				—	
11.3	34	No.				—	
7.4	24	No				—	

sistently because some patients with particularly severe attacks kept taking nitroglycerine or a purine derivative. The 14 patients whose weight was over normal were placed on a reducing diet, yielding about 1000 calories a day; and 4 patients were treated for secondary anemia. The patients have been examined frequently, as a rule at intervals of 1—2 weeks, and always by the writer. Auscultation, electrocardiography, weighing, measuring of the blood pressure, urine analysis and hemoglobin determination have been carried out repeatedly in all the cases. The longest observation period is 83 days.

Therapeutic Results.

Table 2 gives the dosage of cardiferyl in each case, together with the result of the treatment. Of the 22 patients 12 stated their

condition improved under the treatment with cardiferyl, whereas 10 did not notice any change. None of the 12 patients became perfectly free from pain, but the tendency to the attacks was reduced and the attacks themselves were less intense. In all these cases the improvement appeared within the first week of the treatment. The cardiferyl treatment was continued, however, till it seemed reasonably certain that this improvement was not due to continuous remission. Then the patient was given a placebo. This change in treatment was followed by an aggravation of the condition in one patient (No. 11), who failed to return after one week's treatment with the placebo. Another patient (No. 12) was admitted to another hospital before the placebo treatment could be tried, and there he died of coronary thrombosis. In the remaining 10 patients of this group the tendency to attacks did not increase under the placebo treatment, which in most of these cases lasted 3—7 weeks (see Table 2).

The 10 patients who showed no improvement were all given an energetic and protracted treatment. Thus Nos. 13 and 15 received respectively 29.4 g of cardiferyl in 83 days and 21.5 g in 32 days without any effect whatever on the precordial pain. In none of these patients were the attacks particularly severe.

Under this treatment no changes could be demonstrated in the pulse rate, reactions of the pupil, blood pressure or electrocardiogram.

By-effects.

Clerc & Sterne (5) mention that administration of diethylaminoethoxy-2-diphenyl in therapeutic doses occasionally may be associated with the appearance of muscle pain, especially in the biceps, calf of the leg and masseters. In one patient these authors observed phenomena of intoxication. By mistake this patient had taken 20 cg of the drug in one dose. The symptoms seemed at first to remind a great deal of curare poisoning, but shortly after the patient had violent universal convulsions, while he was perfectly clear and the sensibility was normal, the respiration free. The symptoms subsided within an hour, whereafter the patient felt well.

In the present material, 5 patients who were given 30—40 cg of cardiferyl daily have complained of transitory pain in arms and legs. In every instance, these sensations made their appearance after

one day's treatment, and they subsided again as soon as the treatment was discontinued. No symptoms from the central nervous system or from the gastrointestinal tract have been observed, nor convulsions. The writer has examined these patients 1—4 days after the onset of this painful sensation and has not been able to demonstrate any abnormality; in particular, the pulse rate and the reactivity of the pupils have been normal; nor did examination of the blood and urine analysis reveal any abnormality. All these patients have continued taking cardiferyl, though in somewhat smaller doses than before, without any inconvenience whatever.

Comments.

Naturally the estimation of the medicamental treatment of angina pectoris is rendered difficult through the circumstance that the result as a rule has to be evaluated on the basis of the personal judgement of the patient, objective evidence being absent. Besides spontaneous remissions and exacerbation in the course of the disease, various other factors have to be taken into consideration in estimating the therapeutic result. This applies, for instance, to the social position of the patient, changes in the daily regimen, loss of weight, climatic conditions, possibly recovery from some other illness (*e. g.*, anemia) and not least the significance of psychic factors. Not unreasonably, these patients occupy themselves a great deal with their disease and are often depressed because of a more or less pronounced disablement. The interest the physician takes in his patient and his many examinations of them cannot help contributing to kindle their hope of recovery and thus create a brighter look on things. In the more emotional patients, no doubt, these factors will in some degree be decisive of their response to the treatment. But, in the various reports on the treatment of angina pectoris, these conditions are rarely taken into consideration sufficiently. This applies also to the reports cited above. As long as we are not dealing with a causal therapy, the question whether a positive improvement of the patients is due to a certain remedy or to other factors cannot be decided with any degree of certainty without the control employment of placebos.

Of the 12 patients in the present material in whom improvement was obtained in response to the treatment, 2 were severely

attacked (Nos. 2 and 12), while the rest of the cases were of a milde character. Electrocardiography showed repeatedly unquestionable pathological changes in 11 of the patients. Four of these patients may be said to have been distinctly nervous, and their statement concerning the treatment varied somewhat from one examination to the other. From Table 2 it will be noticed that 5 of these 12 patients were losing weight during the treatment, from 2 to 7.7 kg; one of them was at the same time under treatment for diabetes mellitus, with the result that the urine became sugar-free, and in 3 of these same cases the hemoglobin percentage rose as the result of iron therapy. Most likely, these factors helped to make the patients feel better. That the improvement is not attributable to the employment of cardifenyl, moreover, is plainly evident from the fact that the tendency to attacks did not increase under protracted treatment with placebos.

Summary.

An account is given of the treatment of 22 angina pectoris patients with diethylamino-ethoxy-2-diphenyl hydrochloride. Of these patients, 12 stated that the tendency to attacks was reduced in response to the treatment. Replacement of diethylamino-ethoxy-2-diphenyl hydrochloride with placebos did not give any increase in the tendency to attacks; and from these findings the conclusion is drawn that the apparent improvement cannot be ascribable to diethylamino-ethoxy-2-diphenyl hydrochloride.

The remaining 10 patients noticed no change in their condition in spite of intensive treatment.

The longest observation period was 83 days.

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Acute polyradiculitis.

By

H. C. A. LASSEN and MOGENS FOG.

(Submitted for publication March 8, 1943.)

In 1916, on the basis of two cases, Guillain & Barré described a syndrome consisting in an acute polyn neuritis-like lesion with a marked increase in the albumin content of the spinal fluid without any coincident increase in cell count and with a benign course. The authors thought they were able to demonstrate that the pathological process involved the spinal roots as well as the peripheral nerves and the striated muscles. While previously only a few reports had been published on similar morbid features, in the following 25 years a steadily increasing number of cases have been reported which largely correspond to Guillain & Barré's syndrome.

Almost simultaneously with Guillain & Barré — and independently of these authors — Axel Neel (1917) demonstrated a similar case before the Danish Neurological Society and stated that the cause of the disease presumably was to be looked for in a lesion of the nerve-roots. Neel thought it was a matter of an ascending polyradiculitis and that the considerable increase in albumin in the spinal fluid might be explained as attributable to a compression of the veins accompanying the nerve-root.

Here no review will be given of the comprehensive literature on this question; recently de Jong has published a very extensive bibliography. It is to be emphasized, however, that subsequent observations have added various features to the original picture of the syndrome. In the first place, the prognosis has been found not

to be so favorable as shown by Guillain & Barré. In the next place, cases have been observed which in their extension and course correspond precisely to the original cases, whereas they fail to show such a pronounced increase in the albumin content of the spinal fluid as Guillain considered pathognomonic (namely, over ca. 100, in Bisgaard value). Thirdly, cases have been described which did not present the entire symptom complex and have to be designated as abortive forms of the lesion. Finally, polyradiculitis-like cases have been described in which the lesion was very slowly and gradually progressing.

The cause of the lesion has not been settled yet, but most authors agree in looking upon this syndrome as a *nosographic* unity produced by an unknown, presumably ultravisible virus. In recent years, however, several authors (e. g., Pette) have claimed an allergic pathogenesis.

Nowadays the disease is described as Guillain-Barré's syndrome or as polyradiculitis, or polyradiculoneuritis because of the involvement of the peripheral nerves that has been revealed by several pathologic-anatomical examinations. According to Gilpin, Moersch & Kernohan, it is a matter of myeline degeneration in the nerve-roots and peripheral nerves without definite inflammatory changes.

In the following we shall present some cases of the fully developed syndrome together with some abortive and atypical cases observed in the Blegdam Hospital and in the Neurological Department of the Rigshospital, Copenhagen, within the last three years.

The first-mentioned cases were observed mostly in the Blegdam Hospital (infectious diseases), the latter in the Neurological Department.

Even though this lesion is not altogether rare, it is hardly known to any particular extent outside the circle of neurological specialists. Further, in its fully developed form, it has a certain resemblance to poliomyelitis. It is not to be wondered, therefore, that most of these patients have been referred to the Blegdam Hospital (infectious diseases) — and it will be appropriate here first to give a detailed account of a typical instance of the fulminant Landry type of polyradiculitis (Patient No. 7). Later, a couple or more abortive cases will be mentioned.

Case Record of Patient No. 7.

This patient was a man, 60 years old, with a past history of good health — except for an attack of abdominal pain in June 1941. This pain was very intensive, colicky and localized to the lower part of the abdomen. Since then, he has now and then had sensations of compression in the abdomen but no real pain.

On July 10 he had an attack of angina for which he stayed in bed for 5 days, with a rise in temperature up to 38.7. There is said to have been marked enlargement of the lymph glands on the right side of the neck.

One week later, on June 18, the patient had some not particularly characterized sensations in the loins on both sides, radiating down along the posterior aspect of both extremities, even down to the toes and, almost simultaneously, similar sensations in the arms. There was no real pain, but the musculature was tender to pressure. Within a few days his hands and feet began to feel numb and he had tingling paresthesias of the fingers and toes. At the same time, he had a sensation of dryness of the mouth, and his tongue felt swollen; his voice became hoarse and feeble. Then he began to feel a weakness of the legs, and a couple of days later he was hardly able to stand on his feet.

While all this was happening, a couple of days after the appearance of the first neurological symptoms the patient again had pain in the abdomen below the costal margins, and on July 22, that is, 4 days after the appearance of the first paresthesias, he was admitted to the Surgical Department for observation for appendicitis.

Here the muscular power was found to be impaired in all four extremities, and the sensibility was lowered on the soles and palms. During the next 2 days he was getting worse, having now difficulty in swallowing and speaking. He kept complaining of paresthesias of the arms and legs. Physical examination revealed no abnormality in the abdomen. On July 24 a neurologist was summoned and the patient was transferred to the Neurological Department, the Kommune Hospital.

In the Neurol. Dep., 6 days after the onset of the neurological symptoms, the following findings were recorded on examination: The patient is exhausted and sweating. No clinical signs of meningitis. No dyspnea or cyanosis. He is able to knit his brow only with great difficulty; the power of the orbicularis oculi is greatly lowered on both sides; he is unable to close his left eye completely. Paralysis of the right facialis of the mouth, and only slight functional capacity of the left.

Upper extremities: Diffuse symmetrical impairment of muscle power, in particular of the dorsal flexors of the hand.

Abdominal reflexes cannot be elicited.

Lower extremities: Pronounced symmetrical paralysis of the flexor of the knee; paresis of the dorsal flexors of the left foot. Hypesthesia and hypalgesia of the feet and distal half of the legs, besides round the knee-joints and on the posterior surface of the thighs. Plantar reflexes absent.

On the following day, July 25, the hypesthesia and hypalgesia had extended up on the trunk, reaching almost the costal margin. Now signs of respiratory paralysis began to appear, on which account the patient was transferred to the Blegdam Hospital for respirator treatment.

On admission to the Blegdam Hospital, on July 25, the patient was markedly exhausted but not dyspneic or cyanotic. Throat reflexes could not be elicited. The voice was aphonic; the tongue coated and dry. Face mask-like, oligomimic, greasy, glistening with sweat. The patient was perfectly clear and appeared to be mentally normal.

Pupils round, egal, reacting to light and accomodation; eye movements free; field of vision normal.

The brow cannot be knitted; the eyelids cannot be closed; and pouting is impossible.

The sensibility of the face is normal. Voice weak, aphonic. No difficulty in swallowing.

Slight rigidity of the neck and distinct rigidity of the back.

Respiration chiefly abdominal; still, there is also a distinct function of the thoracic respiratory muscles.

Auscultation of the heart and lungs: No abnormality. Pulse 100, regular.

Abdominal reflexes absent.

Sensibility on the trunk normal above the left costal margin and 2 hand's breadth below the right costal margin; distally to this level hypesthesia and hypalgesia.

The upper extremities may be elevated only with difficulty; there is a pronounced, symmetrical impairment of muscular power in all the muscle groups, but most pronounced in the extensors. On the left side, hypalgesia and hypesthesia of the entire dorsal aspect of the arm and on the volar aspect below the elbow. On the right side, uniform hypesthesia and hypalgesia to the shoulder. Biceps and triceps reflexes can be elicited, but the brachioradialis reflexes are absent.

The lower extremities cannot be elevated. There is marked symmetrical impairment of muscular power of all the muscle groups, but no total paralysis of any muscle group. Pronounced hypesthesia and hypalgesia of both lower extremities. Patellar and plantar reflexes cannot be elicited.

The patient was placed in the respirator room, but not in the respirator, as at that point of time he showed no sign of any serious respiratory insufficiency.

At 19²⁰ hours, on the same day, the condition of the patient was suddenly aggravated essentially; the pulse became feeble and frequent, and he died at 19³⁰.

The temperature remained normal throughout the illness.

Special Examinations.

24/7: Blood pressure 140/90. Sedimentation test: 47 mm/1 hr.

25/7: Electrocardiography: No abnormality.

25/7: Ophthalmoscopy: No abnormality.

24/7: Spinal fluid: Pressure 130/100 (before and after evacuation of the fluid); 6/3 mononuclear cells; albumin 40; globulin 1—2.

Autopsy (Dr. Vimtrup) was performed the following day and showed: No sign of pneumonia.

Heart enlarged, myocardium brown, with uneven cut surface showing retracted streaks of connective tissue scattered diffusely throughout. Consistency tough.

Coronary arteries markedly adenomatous; the anterior descending branch divides into two branches, the right of which is calcified and very narrow so that it does not admit the finest probe. The left transverse branch is likewise markedly sclerotic. Moderate atheromatosis and sclerosis of the aorta.

Brain: No macroscopic abnormality.

Nerve-roots hyperemic.

Autopsy diagnosis: Hypertrophy of the heart; Arteriosclerosis of coronary arteries; Fibrosis of the myocardium; Congestion of organs; Hyperemia of the spinal nerve-roots.

Microscopy of the Central Nervous System (Drs. B. Vimtrup and E. Christensen):

The cortex of the brain shows no abnormality except for hyperemia. The basal cerebral ganglia are the site of a very considerable hyperemia. The capillaries in the grey substance are very conspicuous. Red blood cells are seen also outside the capillaries. The nerve-cells show some effacement of the structure of the Nissl substance, and the contours of the cells are poorly defined.

In the lumbar intumescentia the posterior funiculi show degeneration of the medullary sheaths, just posteriorly to the horn. The lateral fasciculi show superficially degeneration of smaller groups of medullary sheaths interspersed with well-preserved medullary sheaths.

There is a rather pronounced pericellular oedema of the grey substance, especially round the nerve-cells in the anterior horns. These nerve-cells are swollen, showing chromatolysis and eccentric location of the nuclei. No round-cell infiltration is seen in the grey substance or elsewhere in the cord, whereas accumulation of lymphocytes is seen here and there in the meninges.

The anterior as well as the posterior nerve-roots present a very pronounced hyperemia. The blood are dilated and filled with blood. A moderate degree of medullary sheath degeneration is seen in the posterior roots.

Also the spinal ganglia from the lumbar region show considerable hyperemia. Several of the wide blood vessels contain a great many polymorphonuclear leucocytes, which here appear to be just as numerous as the red blood cells. Further, leucocytes are also seen extravascularly, as well as several mononuclear cells resembling leucocytes. Some of the nerve-cells are well-preserved, others have undergone degenerative changes, with large amount of pigment in crescent heaps peripherally in the cells, dust-

like degeneration of the Nissl substance, and some shrinkage of the cells, while the «mantel-cells» are predominant at the wide space round these cells. Similar but less pronounced changes are seen in a ganglion from the thoracic region.

Microscopic diagnosis: Polyradiculitis (radiculo-meningomyelitis).

For the sake of completeness and in order to illustrate the fairly thorough etiological studies that have been carried out in the Blegdam Hospital concerning this disease, it will be appropriate also to give a detailed account of the animal experiments performed in this case. (The summary of the animal experiments in general will be given in the discussion of the etiology.)

At the autopsy the entire spinal cord was removed together with the appending spinal ganglia and the brain stem — as far as possible under aseptic precautions.

The specimen was divided into 3 parts: 1) nerve-roots and spinal ganglia; 2) spinal cord; 3) medulla oblongata and pons.

1. The nerve-roots and spinal ganglia were ground with sterile sand in a mortar and sterile salt solution was added to make an emulsion, which was centrifuged lightly in order to separate all the larger particles. Cultures from the supernatant turbid fluid yielded growth of staphylococci and streptococci but not in any great amount.

As previous experiments had shown that emulsions of this kind may be filtered through bacterial filters only with great difficulty, and as we further were afraid that such filtration would retain the greater part of any virus that possibly might be present in the fluid, we decided to inoculate the animals with this unsterile emulsion.

On 26/7 — the day after the death of the patient — the emulsion was injected into the following animals:

- 1 macaco Rhesus monkey; 2 cm³ intracerebrally.
- 7 mice; 0.03 cm³ intracerebrally.
- 2 rabbits; 0.5 cm³ intracerebrally.
- 1 guinea-pig; 0.5 cm³ intracerebrally.

Some of these animals — the two rabbits and three mice — died in the next few days of purulent meningitis. All the others, including the macaco monkey remained perfectly well and free from symptoms.

After 12 days, 2 of the surviving mice were killed. The brain which was removed sterilely looked normal. Both brains were emulsified and injected intracerebrally into a group of mice. None

of these 5 mice got any symptoms; they all remained perfectly well during the following months.

2. From the spinal cord a similar emulsion was prepared. It, too, proved to be contaminated with staphylococci and streptococci. The emulsion was injected intracerebrally into 1 rabbit, 1 guinea-pig and 7 mice. Of these animals 2 mice died in the next couple of days from purulent meningitis. All the other animals remained well and symptom-free.

3. A similar emulsion was prepared from the medulla oblongata and pons.

The emulsion was injected into 5 mice, 1 rabbit and 1 guinea-pig. In no instance did there appear any sign of a stroke.

Summary of the Case.

A man, aged 60, with past history of good health, has an attack of angina in July 1941. On 18/7 he has paresthesias over the loins radiating down in the legs and paresthesias of the arms.

In the next few days, muscular weakness develops in the legs.

As now, in addition, the patient has pain in the abdomen he is admitted to a surgical department for appendicitis. Here, no sign of appendicitis can be made out but signs of a neurological lesion are ascertained; and he is transferred to the Neurological Department on 24/7.

His illness progresses rapidly, terminating in death 1 ½ days later.

Clinical Findings: Bilateral facial paralysis;

tetraplegia, especially of the lower extremities;

sensory disturbances of peripheral type;

absence of reflexes;

rigidity of the neck and back;

moderate functional impairment of the thoracic respiratory muscles.

The patient dies suddenly on 25/7 after 8 days' illness, possibly from sudden central respiratory paralysis, possibly from insufficiency of the coronary circulation.

The temperature was normal throughout the course. The spinal fluid showed 6/3 mononuclear cells, albumin 40, and globulin 1—2.

Autopsy revealed a pronounced sclerosis of the coronary arteries and fibrosis of the myocardium, besides hyperemia round the nerve-roots and interspinal ganglia, especially in the lumbar region.

The histological examination of the central nervous system showed hyperemia of the basal cerebral ganglia and slight degenerative changes of the nerve-cells. The spinal nerve-roots showed a very pronounced hyperemia, demyelination and leucocyte infiltration together with degenerative changes in the nerve-cells.

Inoculation of various species of animals with emulsions made from the central nervous system failed to give any take.

It is to be emphasized that the case described here is by no means unique; it has been cited merely because it is particularly characteristic of the lesion.

As the disease here described, as mentioned, in some respects has a not inconsiderable resemblance to acute anterior poliomyelitis, it will be appropriate, we think, here to point out the points of resemblance between the two diseases and especially their points of difference.

As in practice there is no possibility in the two diseases to demonstrate the etiological agent — indeed, no such agent has ever yet been demonstrated in polyradiculitis, their differentiation will for the present have to be based entirely upon clinical and possibly epidemiological differences.

Thus we have no established data as to the range of clinical variations possible within the individual etiological unit — that is, provided that polyradiculitis represents a nosological unity *distinctly* different from poliomyelitis. Our animal experiments (the negative experiments with inoculation of monkeys) might perhaps be taken to point in that direction. At present the only possibility is: that histological studies on the central nervous system may be able to help us gain a survey of the range of clinical variations that may be encountered in either the two diseases. But, it is true, this will depend on whether the histological examination will be able with certainty to differentiate between the two lesions — something that is not quite certain. For the present, therefore, we have to maintain the decidedly clinical classification and as far as possible take into account the information we may gain about the localization of the morbid changes in the central nervous system which the microscopic examination can give us.

As to the *age* of the patients, polyradiculitis is rare in children under 10 years, most frequent in the younger adults but may be

seen also in elderly. Poliomyelitis — in particular outside epidemics proper — is preponderantly a disease of children and is seen but very seldom in persons over 40.

Epidemiology. — No seasonal variation has been demonstrated for polyradiculitis. Still, our small materials are suggestive of some accumulation of cases in the months of the autumn. No epidemic occurrences have been reported, although some local accumulation of cases has been observed.

Poliomyelitis, on the other hand, shows a very pronounced accumulation in the months of the autumn; indeed, as is well known, its occurrence may sometimes have a pronounced epidemic character.

Prodromal Symptoms are often absent in polyradiculitis; now and then, however, there is an «influenza»-like precursory stage, lasting from a few days to a couple of weeks, before the appearance of the first neurological symptoms.

In poliomyelitis, on the other hand, prodromal symptoms are common before the meningeal stage, appearing as a slight rise in temperature, headache and, not infrequently, gastro-intestinal symptoms.

Initial Symptoms. — In typical cases the initial symptoms of the two diseases are widely different.

In polyradiculitis the first neurological symptom consists most often in paresthesias of the extremities, especially the lower, sometimes lancinating pains. Shortly after, or simultaneously with this, the patients have a sensation of weakness in the extremities and now there are demonstrable, symmetrical, diffuse, partial pareses in the extremities without a pronounced loss of tonus. The clinical symptoms of meningitis are nearly always inconspicuous. There is no hyperesthesia of the skin. In typical cases, in the absence of complications, the patients have no fever.

The poliomyelitis patients present an entirely different picture in the initial stage. They are febrile and have almost invariably pronounced meningeal symptoms, often marked cutaneous hyperesthesia, but no paresthesias. The pareses are asymmetrical, selective and associated with a pronounced loss of tonus. Yet, sometimes — e. g., in Copenhagen, in summer 1942 — we meet with an accumulation of cases of poliomyelitis with symmetrical, diffuse pareses in the extremities, either in the form of paraplegia inferior

or as tetraplegia. But most of these cases which may show a considerable resemblance to polyradiculitis present, in addition, a few or several of the other clinical features mentioned below as characteristic of poliomyelitis. Occasionally the clinical differential diagnosis between poliomyelitis and polyradiculitis may be well nigh impossible. Thus, in the Blegdam Hospital in the past year we have seen a few cases which clinically presented all the essential characteristics of polyradiculitis, whereas the histological examination was most suggestive of poliomyelitis.

Course. In polyradiculitis it is characteristic that the pareses within the individual region are progressing relatively slowly, reaching their maximal intensity only after some days or weeks, and they remain diffuse, symmetrical and incomplete. The maximal extension is reached only after several days or even after weeks; and some tonus is nearly always preserved in the affected musculature. Tetraplegia occurs very often; hypesthesia and hypalgesia may be demonstrated not infrequently. If the case remains uncomplicated, its entire course is afebrile.

In poliomyelitis the pareses within the individual region nearly always attain their maximal degree of intensity rapidly — at the most within a day or two; and they nearly always remain elective and asymmetrical; not infrequently they are total, with a complete loss of tonus. The maximal extension of the paralysis is reached almost invariably within a couple of days at the most after the first signs of the paralysis are observed. Once the progression of the lesion has stopped for two or three days, it happens but very seldom that it progresses anew. Tetraplegia is rare in poliomyelitis; hypesthesia and hypalgesia can practically never be demonstrated. In an overwhelming majority of the cases the temperature is elevated distinctly the first 3—5 days.

In polyradiculitis an eventual improvement may appear in a few days after the pareses have stopped spreading. The improvement progresses gradually and leads always to full restitution — or almost complete restitution in from some months to about one year.

In poliomyelitis, on the other hand, the eventual improvement is irregular. If there appears any essential improvement of the affected musculature, it will mostly make its appearance very early, within the first days. After this, the progress the patient will

make will be very slow and often slight. In many cases there will be extensive permanent paralysis with marked muscular atrophy.

Also the *spinal fluid findings* show characteristic differences in the two diseases. In patients with polyradiculitis, in the early stage of the disease there will usually be no increase in the cell content, or merely a few mononuclear cells, and the protein values may be normal, though often they are increased. After some weeks, the cell count is normal, but sometimes associated with high albumin and globulin values (dissociation albumino-cytologique).

In poliomyelitis it is the general rule that the spinal fluid in the paralytic cases contains several cells, nearly always over 50/3, but seldom over 1000 cells per 3 mm³. Most of the cells are mononuclears, though in the first days of the disease there will often be some polynuclear leucocytes. The protein values are normal or slightly increased. The pleocytosis decreases gradually, although it often is demonstrable for several weeks. In the later stage of the disease there may be some increase in the protein content of the spinal fluid, especially if the initial cell count was high.

The *prognosis* in the here mentioned fully developed form of polyradiculitis cannot be said to be good, as 10 of our 15 patients with this type of the disease died. But if the patient gets over the critical point the prognosis as to the pareses is good.

In poliomyelitis the prognosis is highly dependent upon the character of the epidemic. Largely, the case mortality may be said to decrease with the increasing extension of an epidemic of poliomyelitis. Still, epidemics occur now and then in which the bulbar symptoms are conspicuous features and here the case mortality may be up to 25 %. As to the poliomyelitic pareses the prognosis is doubtful — and poor unless an essential improvement makes its appearance early in the course of the case.

In both diseases the most frequent cause of death is respiratory paralysis with complicating pneumonia.

Symptoms, objective findings and a few other data concerning our 15 patients with acute extensive polyradiculitis are recorded in Table 1.

Of this material, 10 patients come from the Blegdam Hospital, 3 from the Neurol. Dep. of the Rigshospital and 2 from other hospitals.

The sex distribution of the patients appears to show some male preponderance. — 10 men and 5 women. The age distribution

Table
Fifteen patients with acute extensive

	Number	1	2	3	4	5
	Sex	m	f	m	f	m
	Age	28	41	23	7	45
	Onset in month	IX	VI	IX	XI	VIII
	Prodromata	+	÷	÷	÷	÷
Initial symptoms	Paresthesias	+	+	+	?	+
	Pain	÷	÷	+	+	+
	Pareses of cranial nerves	÷	÷	÷	÷	÷
	Pareses of the extremities	+	+	+	+	+
	Paresis of the bladder	+	÷	÷	÷	÷
Symptoms at first examination	Day of illness	5	1	4	2	10
	Pareses of cranial nerves	÷	÷	÷	÷	÷
	Pareses of upper extremities +: r. or l., ++: r. and l.	+	++	++	++	++
	Pareses of lower extremities +: r. or l., ++: r. and l.	+	++	++	++	+(+)
	Disturbances of sphincters	+	+	÷	÷	÷
	Sensory disturbances	+	+	+	+	÷
	Abnormal reflexes	+	+	+	+	+
	Rigidity of neck and back	+	+	÷	+	(+)
Maximal extension	Pareses of cranial nerves	÷	+	÷	+	+
	Bulbar involvement	÷	÷	÷	+	÷
	Respiratory paralysis	+	÷	+	+	÷
	Tetraplegia	+	+	+	+	+
	Disturbances of sphincters	+	+	+	÷	÷
	Course afebrile	÷	+	÷	÷	÷
	Onset afebrile—fever because of complications	+		+	+	+
	Duration of progression (days)	until death	10—12	until death	until death	until death
	Improvement after (days)	÷	14—21	÷	÷	÷
Last exam.	Reexamination after (months)		30			
	No or insignificant remnants		+			
	Moderate or severe remnants					
Spinal fluid.	Day of illness	5—7	8—11	6	2	9—10
	Cell count	16—10	16—3	5	1	0—11
	Total protein	10—30	20—<10	>30	<10	80—70
Cause of death	Died on day of illness	+8		+19	+4	+11
	Improved (i)		i			
	Respiratory paralysis	+		+	+	+
	Pneumonia	+		+	+	+?

1.

polyradiculitis — symptoms and signs.

6 m 13 VI ÷	7 m 60 VII +	8 f 50 I ÷	9 m 36 V +	10 m 7 VI ÷	11 m 37 VII ÷	12 m 36 VII +	13 f 14 XII +	14 m 55 VII ÷	15 f 41 III +
÷	+	+	+	+	+	+	+	+	+
+	÷	+	÷	+	÷	÷	+	+	÷
÷	÷	÷	÷	÷	÷	÷	÷	+	÷
+	+	+	+	+	+	+	+	÷	+
÷	÷	÷	÷	+	÷	÷	+	÷	(+)
7 ÷	5 +	9 ÷	5 ÷	10 ÷	5 ÷	6 ÷	abt. 120 ÷	abt. 35 +	abt. 50 ÷
++	++	++	+	++	++	++	++	÷	++
++	++	++	++	++	++	++	++	÷	++
÷	÷	÷	÷	÷	÷	÷	+	÷	÷
÷	+	+	÷	+	+	+	+	+	+
÷	+	+	÷	+	+	+	+	(+)	+
+	+	÷?	÷	(+)	(+)	÷	+	÷	?
÷	+	÷	+	÷	÷	÷	÷	+	÷
÷	+	+	+	+	+	+	÷	÷	÷
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÷	÷	+	+	÷	÷	÷	+	÷	+
+	+	+	÷	+	+	÷	+	÷	÷
<7 few 20 ÷	until death ÷	until death ÷	until death ÷	until death ÷	until death ÷	until death ÷	abt. 14 14 9 +	abt. 14 14 2 +	abt. 35 abt. 35 6 +
7—40 40—23 20—?	7 6 40	11 8 30		7 4 60	5—7 3—16 10—20	7 2 <10	9—42 9—92 10—40	?—42 9—7 90—90	28—50 3—0 90—115
i	+8	+11	+18	+15	+9	+8			
	+?	+	+	+	+	+	i	i	i
	÷	÷	+	÷	÷	+			

ranges from 7 to 60 years and is fairly equal; two-fifths of the patients were over 40 years.

Turning to the seasonal distribution of the cases we find that 2 cases commenced in the first quarter of the year, 4 in the second, 7 in the third, and 2 in the fourth. So it might look as if a certain accumulation of cases takes place in the summer and autumn (of the 4 cases in the second quarter, 3 had their onset in June).

Prodromata. — In 9 cases there were no prodromal symptoms (i. e., none were observed); in the remaining 6 cases there was a precursory stage resembling «influenza» or a cold, sometimes with a little fever, from a couple of days to a couple of weeks before the appearance of the initial symptoms proper.

Initial Symptoms. — Paresthesias of the extremities were recorded in 13 cases — appearing most often in the lower extremities first. Pain in the extremities was present in 8 cases, often of a radiating character (referred especially to the lower extremities). In rapid connection herewith, sometimes within a few hours, sometimes after a couple of days, the patients noticed a beginning loss of muscular power in the extremities, most often first in both lower extremities at the same time and, after this, attacking both upper extremities. Sometimes the pain commenced in one extremity, and then is spread to the others.

In 4 cases retention of the urine was recorded in the initial stage.

Objective Findings at the 1st physical examination. — In the 12 cases which did not come from the Neurol. Dep. of the Rigshospital, this examination was performed within the first 10 days of illness, in 7 cases within the first 5 days of illness. In the cases from the Neurol. Dep. of the Rigshospital, the 1st physical examination was made somewhat later, from 1 to 4 months after the onset of illness.

Two patients had cranial-nerve paralysis, involving in both cases the facial nerve.

As to the pareses of the extremities, tetraplegia was present in 12 cases — often slight, but not infrequently massive. The pareses were always markedly symmetrical and diffuse, but not infrequently more pronounced in certain groups of muscles (e. g., the extensors of the arms, the dorsal flexors of the feet). As a rule these pareses developed in a couple of days, sometimes in a few weeks.

Sensory disturbances were demonstrated by the 1st physical examination in 11 cases, and in all but two of the patients reflex disturbances were found, most often absence of deep reflexes.

Clinical signs of meningitis — rigidity of the neck and back, positive Kernig's sign — were present in 9 patients, but only in a minor degree.

Fever. — It is characteristic that these patients are afebrile when the neurological symptoms set in; and in many cases — including all those which do not terminate fatally — the patients remain afebrile. In the patients who died in the acute stage of the disease there is most often a rise in temperature, usually quite considerable, in the last days before death. These patients die of pneumonia. A couple of the patients who died had no fever at all. None of our 15 patients showed any temperature over 38° until the last few days before their death.

Duration of the Progression. — In the patients who get over their illness the neurological symptoms usually keep progressing only for a few days or up to a couple of weeks, in rare instances for about one month. In the fatal cases the progression of the symptoms usually keeps on till exitus. Of these patients 5 died before the 10' day of illness, the other 5 before the 20' day of illness.

Maximal Extension. — In 14 of the patients the height of the disease was associated with pronounced tetraplegia. In 1 patient, who was first examined 5 weeks after the onset, there were ataxia of the lower extremities, dysesthesia of the hands and legs.

Of cranial nerve pareses, the muscles of the eye were involved in 1 patient; facialis paresis was demonstrated in 6, deglutition paresis and difficulty of speech in 7, who all died. Respiratory paralysis was observed in 11 patients, 10 of whom died, and sphincter paralysis in 7.

Findings at the Last Examination. — Altogether 5 patients were discharged and reexamined from 1 ½ months to 2 years after. They had all improved quite considerably, most of them presenting merely some insignificant remnants of the lesion; in one case the remnants were of a moderate degree. Only one of these patients was quite free from any remnant of the disease. The others showed impairment of the muscle power in one or more extremities, remnants of facial paralysis, or peripheral dysesthesia.

Spinal Fluid. — On the patients from the Blegdam Hospital, lumbar puncture was nearly always performed only within the first couple of weeks of illness. On the patients from the Neurol. Dep. of the Rigshospital, lumbar puncture was performed only at a later stage of the disease. In one case lumbar puncture was omitted on account of particular circumstances.

Characteristic features: Early in the disease the cell count is increased but slightly or not at all — 14 out of the 15 patients showed less than 20/3 cells, while 1 showed 40/3 — always mononuclear cells exclusively. The cell count returns nearly always to a normal level very rapidly, in a couple of days to a few weeks.

Total protein: In the early stage — *i. e.*, within the first 8 days of illness — the protein values are normal or slightly increased (albumin 40—50), but later, as the cell count falls off towards a normal level, there is sometimes an additional rise in the albumin and globulin contents. Thus, the characteristic »dissociation in the spinal fluid» which has been emphasized so strongly by Guillain & Barré, is most often present, especially later in the course of the disease. When we have not been able more often to demonstrate a definite »dissociation albumino-cytologique» in the spinal fluid, it is possibly because in most of our cases a lumbar puncture was performed only early in the disease.

Of the 15 patients, 10 died; and none of these fatal cases was observed in the Neurol. Dep. of the Rigshospital.

Causes of Death: Respiratory paralysis and pneumonia in 5 cases; isolated (central ?) respiratory paralysis in 4 patients with bulbar symptoms; and respiratory paralysis in 1 patient with bulbar symptoms, who also presented advanced coronary sclerosis. So, more or less pronounced paralysis of the respiratory muscles was present in all the fatal cases.

All the cases mentioned so far have been stamped by polyradicular features: symptoms from nerve-roots in several segments, sometimes both cranial nerves and the nerves of the upper and lower extremities. The clinical features that unite these cases into a group by themselves are the radicular character of the symptoms and the characteristic rapid course of the lesion — to exitus, improvement or eventual recovery.

Sometimes, however, cases are encountered with radicular sym-

ptoms and presenting the same course, but with the symptoms localized exclusively to the lower extremities. In the Neurol. Dep. of the Rigshospital 8 cases of this kind have been observed, in which the disease commenced in 1939—40. These patients were 3 women and 5 men, aged from 14 to 59 years. In 6 of these cases the disease made its appearance from the latter part of August to the beginning of October. In all these cases the onset was acute, with pain in the loins and lower extremities, which soon — at the most, within a few days — was followed by paresis in the lower extremities, from fairly moderate paresis to complete paralysis. In addition, sphincter disturbances were present in about one-half of the cases. After the extension of the pareses had reached its maximum — with one exception, within 1 week — signs of improvement turned up rapidly, and on reexamination, from 4 to 18 months after the onset, these patients all showed recovery or considerable improvement. Only the patient who was most strongly affected has yet (after 14 months) a considerable impairment of the muscular power of the legs.

Owing to the conditions governing admission to the hospital, the first thorough physical examination of these patients was made at a relatively late juncture, from 18 days to 4 months after the onset. At this point of time many of the patients had improved considerably; thus the pareses had disappeared in 3 of them. But in most of them there still remained a slight or moderate degree of muscular atrophy and sensory disturbances; and they all showed weakening of the deep reflexes on the legs. On the other hand, none of these patients presented any symptoms from the upper extremities or cranial nerves — nor had such symptoms ever been present.

The aspects of the spinal fluid in these cases are difficult to judge because the lumbar puncture was performed so late. Only 2 patients showed normal protein values; the others showed values between 30 and 100 (Bisgaard).

For illustration, the history of a typical case will be cited briefly.

A woman, 30 years old, with a past history of good health had suddenly, on August 20, pain and backache over the loins. There had been no prodromata, and she had no fever. Four days later the pain was radiating down in the posterior aspects of the thighs and

legs; she had paresthesias, and numbness of the buttocks. In the following days, paresis appeared in both legs. 25 days after the onset she had alvine incontinence, which lasted for a few days.

Physical examination, 5 weeks after the onset, showed slight atrophy of both legs, paresis of the dorsal flexors of the feet and, in a lesser degree, of the plantar flexors. Patellar, plantar and Achilles reflexes absent. Symmetrical impairment of the sensibility round the anus and laterally on the legs.

In this case the disease was progressing for about 1 week, and then remained stationary for about 1 month, whereafter the patient improved rapidly.

The spinal fluid, 2 weeks after the onset, showed 7/3 cells, globulin 3, and albumin 100. Three weeks later: 2/3 cells, globulin 4, albumin 35—40.

One year after the onset, the patient presented no paresis whatever, and had no complaint of pain in the legs. The Achilles reflexes were still absent.

This case has to be classified as a clear-cut instance of polyradiculitis caudae equinae.

A surprisingly rapid progression of the symptoms was seen in the case of a boy, 14 years old, who in the night of August 25, without any preceding ailment, suddenly had intense lancinating pain in both legs. Next morning his legs were completely paralyzed, the hip regions were altogether numb, and the urination was sluggish. At this early juncture, the disease had already reached its maximal intensity. A couple of days later, the symptoms commenced to subside.

Physical examination on the 18' day of illness revealed no abnormality of the cranial nerves or upper extremities, but pareses of the extensors of the knees and of the dorsal and plantar flexors. The tonus was normal, but there was a slight diffuse atrophy of the musculature of the legs, together with sensory disturbances corresponding to the lower sacral segments. The plantar reflexes were absent. Examination of the spinal fluid about 3 weeks after the onset showed 7/3 cells, globulin 5—6, albumin 60—65; 5 months after the onset: 2/3 cells, globulin 1 and albumin 15.

On reexamination, 7 months after the acute stage, there remained merely a bilateral drop-foot and slight sensory disturbances.

This case, too, has to be classified as an instance of cauda equina radiculitis.

In our opinion there can be no doubt that in these cases we meet with a lesion that has to be grouped together with the above-mentioned cases of extensive acute polyradiculitis. Here, however, the process has stopped, with the affection of the cauda equina — a nosographic picture we have designated as polyradiculitis caudae equinae.

Now and then, however, one meets with morbid conditions deviating from the ones described so far with regard to the extension of the process and yet presenting so many points of resemblance to acute polyradiculitis that it seems most reasonable to take them as variants of the same disease.

A man, aged 61, had an attack of «influenza» — in March — for which he stayed in bed for 8 days; the temperature was not measured. Then he got up, but 3 days later he had pain over the loins, his legs felt cold, he had paresthesias of the legs, especially the right, and also the right leg was enfeebled. Two days later he had peripheral facial paralysis on the right side. Subsequently there developed a transitory peripheral facial paralysis on the left side, bilateral impairment of the hearing, paresis of the flexion and extension of the knees, flaccid paralysis of the crural muscles, especially on the right side, and abolition of the knee-jerk on the right side.

In this case the disease progressed to its maximum in a couple of days and then remained stationary for about one month, whereafter the patient improved.

Examination of the spinal fluid on the 19' day of illness showed 3/3 cells, globulin > 10 , and albumin 40; on the 42' day of illness, 1/3 cell, globulin 4, and albumin 45.

Here we see the same rapid development of the lesion, with symptoms of presumably radicular character, localized in part to the 7' and 8' cranial nerves, partly to the lower extremities.

Another instance of atypical polyradiculitis is to be cited briefly:

In March, a man, 48 years old, suddenly had an attack of occipital headache for 1 week (without any preceding ailment); in the following week he had «an attack of rheumatism» in the left shoulder, accompanied by paresthesias of the left index finger. One

week later there was impairment of vision in the left eye. No sphincter disturbances.

Physical examination 3 months after the onset showed choked discs, weakened biceps reflexes on the left side, atrophy and paralysis of the left triceps.

In this case the disease progressed to its maximum in 2 days; one week later, however, the vision commenced to be impaired. The choked discs subsided in 4—5 months.

Reexamination, 11 months after the onset, showed complete recovery.

In this case there are no symptoms from the cranial nerves, but transitory choked discs associated with radicular symptoms in the upper extremities. The choked discs have to be looked upon as brought about by a leptomeningitis, an arachnoiditis in the posterior cranial fossa with transitory occlusion of the basal foramina. Here we come near the cases which in this country have been described by Einar Sørensen under the designation: basal arachnoiditis of the brain.

Naturally it is impossible to say whether all these more or less divergent cases represent one etiological unity. But this is suggested by the symptomatology. Accordingly, many of the patients described by Viggo Christiansen under the diagnosis radiculomeningomyelitis would be referable to the acute polyradiculitis group.

On the other hand, we think, it will be unjustified — as suggested by various authors, including de Jong — to let this group cover also morbid conditions characterized by radicular symptoms and increase in the protein content of the spinal fluid, *but* with a slow development of the lesion, which most often keeps progressing for several months, and often takes a remittent course.

Here we are dealing with cases which have to be designated as chronic intermittent adhesive arachnoiditis or, preferably, leptomeningitis. From our experiences so far, there is nothing to indicate that such a slowly progressing lesion, with a tendency to relapse, might be of the same origin as the disease we have been dealing with here. But, of course, no definite statement can be made in this respect, as the etiology of these morbid conditions is still obscure.

For the present, then, as has been emphasized several times,

we will restrict the clinical diagnosis acute polyradiculitis (polyradiculoneuritis) to cases in which the disease develops within a few days to a couple of weeks, with pain, paresthesias, flaccid pareses, weakened deep reflexes and sensory disturbances of radicular character, corresponding to a greater or smaller number of spinal nerve-roots, most often associated with an early considerable increase in the protein content of the spinal fluid — and with a tendency to improvement or recovery without any relapse if the acute stage is overcome.

As mentioned, of the 10 patients admitted to the Blegdam Hospital, 8 died with acute extensive polyradiculitis. Autopsy was performed in 6 of these cases, with a fairly thorough histological examination of the central nervous system.

Macroscopically the central nervous system presented no conspicuous changes, though a striking hyperemia was noted in several cases.

The *histological examination*, on the whole has shown some fairly uniform pictures that may be summarized as follows:

Meninges: Hyperemia, sometimes accumulation of lymphocytes round the blood vessels.

Nerve-roots: Hyperemia, accumulation of lymphocytes, medullary-sheath degeneration, and sometimes destruction of axis-cylinders.

Spinal Ganglia: Hyperemia, interstitial infiltration with mononuclear cells, medullary-sheath degeneration, accumulation of pigment in the nerve-cells, and dusty degeneration of the Nissl substance, sometimes destruction of nerve cells.

Spinal Cord: Round-cell infiltration round the blood vessels, sometimes an increase in glia cells, medullary sheath degeneration and, in several specimens, swollen and poorly staining nerve cells.

Pons and Basal Ganglia of the Brain: Hyperemia and, in a few specimens, effacement of the Nissl substance and indistinct contours of the nerve cells.

According to these histological findings the correct designation for this type of the disease would be acute radiculo-meningomyelitis. But, as «polyradiculitis» has become naturalized to some extent in the international medical literature, we have found it more practical and convenient to maintain this term.

Finally, a few words about the *treatment* of the severe cases of the disease.

For the acute affection there is no causal therapy, and hence it is not possible to prevent the appearance of respiratory paralysis. Another question is whether it may be possible to avoid the occurrence of pulmonary complications in these exhausted cyanotic patients with more or less pronounced respiratory paralysis. We have treated several of our patients by placing them in the respirator, and we have applied suction drainage to the larynx in order to remove the large amounts of foamy fluid which these patients are not able to bring up by themselves. We have given them sulfathiazole early — in order, if possible, to suppress a beginning pneumonic process. These measures appear to have been futile in every instance. For once this phase is reached, the disease has invariably taken its inexorable course — just as happens in nearly all cases of poliomyelitis with bulbar symptoms. Therefore, we cannot subscribe to the prevailing view that the prognosis of acute polyradiculitis is good, at any rate not in cases where the disease is extensive. Of our 15 patients with this type of polyradiculitis or radiculo-meningomyelitis 10 died.

As to the later treatment, it does not differ from the carefully supporting and mitigating treatment usually employed in poliomyelitis when the acute phase is over. The prognosis with regard to the paralysis being better in polyradiculitis than in poliomyelitis, no doubt there will seldom be any indication for surgical orthopedic measures; at any rate, no such treatment has been required in any of our cases.

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Etiological studies on acute polyradiculitis (radiculo-meningo-myelitis) of the Landry type.

**Experiments on Demonstration of a Virus — with
Negative Outcome.**

By

H. C. A. LASSEN, JOHS. IPSEN and JENS BANG.

(Submitted for publication March 8, 1943).

In the Blegdam Hospital, since 1939 we have observed 10 cases of acute polyradiculitis, most of them taking the Landry type of course, and most often showing Guillain-Barré's dissociation albumino-cytologique in the spinal fluid.

As the disease has not been diagnosed in this hospital prior to that point of time, its not altogether infrequent occurrence in the later years is presumably to be taken to indicate that acute polyradiculitis for the time being is more frequent in this country than previously — something that is quite in keeping with the experiences of other authors (Pette, van Bogaert).

Numerous authors have advocated the view that certain forms of acute polyradiculitis are due to an infectious agent, probably an ultra-filtrable virus (*e. g.*, Guillain; van Bogaert & Maere; Roger & Boudouresque; Giraud & Boudouresque; Gilpin, Moersch & Kernohan; Petter & Környey). This view, however, is based but to a very slight extent on experimental studies. For, as far as we have been able to find out, only a few experiments have been reported (Demme) that were aimed directly at the demonstration of a virus, and none of them gave a positive result.

Our material comprises 5 patients, one of whom survived, while the remaining 4 died, three of them with symptoms of respiratory insufficiency. From the first patient, therefore, only spinal fluid was employed as experimental material; from the others, in addition to the spinal fluid, emulsions were made from various parts of the central nervous system for inoculation of the animals.

Patient No. 1. Woman, 41 years old.

In autumn 1935, hospitalized for psychogenic depression. In September 1939, severe eruption of herpes genitalis; relapse in February 1940.

19/6/40: Admitted to a surgical clinic for fibroma of the uterus (?), and treated with curettage.. During her stay here, on 23/6, the patient complained of paresthesias of the extremities. Next day a diffuse symmetrical impairment of muscular power was ascertained on both sides, together with absence of tendon reflexes, ataxia and lowered sensibility of the lower extremities; the temperature did not rise above 37.5.

During the following days there further developed paralysis of the right abducens and ptosis of the left upper eyelid. On 13/6 she had difficulty in breathing, on which account she was transferred to the Blegdam Hospital for respirator treatment.

1/7: Complete symmetrical paralysis of the lower extremities, abolition of all reflexes, and very pronounced hypalgesia. Considerable impairment of the muscular power of the arms, with abolition of the reflexes here, and distinct hypesthesia. Now, also peripheral facial paralysis on the right side, and some rigidity of the neck.

2/7: Paralysis of the sphincter ani.

Beginning improvement about 2 weeks later.

29/8: The patient is able to walk fairly well in a go-cart, but she still has paresthesias of the feet.

10/10: Discharged from the hospital. Remnants of the right facialis paresis. Muscular power of the arms normal, but reflexes weak. Muscular power of the lower extremities still a little impaired; reflexes weak.

Reexamination, on 4/2/43: Feeling well; still a very slight distortion of the face; gait normal — she has been able to walk up to 20 km at a stretch.

No muscular atrophy, reflexes normal.

Spinal fluid, 30/6: Pressure 330/140, slightly increased albumin and globulin values (alb. 20, glob. 1—2), 16/3 mononuclear cells. Wassermann negative.

• • 3/7: Pressure 250/130, albumin 10, globulin 0, 3/3 mononuclear cells.

Animal Experiment: The spinal fluid obtained on 3/7 was used for inoculation of the following animals (shortly after its withdrawal):

1 rabbit: 1 cm³ intracerebrally.

1 " Instillation in the eyes after corneal scarification.

6 mice: 0.03 cm³ intracerebrally.

All the inoculated animals remained well during the following months.

Patient No. 2. Man, aged 23.

In spring 1940, lymphogranulomatosis was diagnosed, for which he was under treatment in the Radium Station, Copenhagen, 29/8—13/9, 1940.

30/9: Paresthesias in various parts of the body; feeling very weak. During the following days the weakness of his legs was increasing, and he had tingling paresthesias of the hands and arms, a little later, of the legs too. On 2/10 the patient was able to walk only with the support of two canes.

Up to this point of time there had been no elevation of the temperature.

3/10: Admitted to the Helsingør Hospital. Temperature 37.3°. Pharyngeal reflexes apparently absent. Muscular power equally impaired in all four extremities, and tingling paresthesias still present. The pareses are symmetrical, incomplete, more pronounced distally; tendon reflexes absent. No rigidity of the neck or back. Sensibility apparently lowered on the lateral aspects of the right leg, otherwise normal.

7/10: Difficulty in voiding. Muscular weakness of the arms increased, and now there is almost complete paralysis of all four extremities. Now the surface sensibility is slightly lowered, the deep sensibility markedly impaired.

14/10: Paresthesias of the hands still present.

16/10: Beginning difficulty in breathing, giving an impression of paralysis of the diaphragm.

17/10: Admitted to the Blegdam Hospital, and placed at once in the respirator. Profuse secretion of mucus from the upper respiratory passages (suction drainage applied). He is cyanotic and has a cold sweat; he is unable to cough. Sensibility now markedly impaired (prick, touch).

18/10: The patient dies suddenly at 9 a. m. after a total of about 19 days of illness — pneumonia (?), respiratory paralysis.

The temperature remained normal until 10/10: then it kept at a level of between 37° and 38° until 17/10.

On admission to the Blegdam Hospital on 17/10, it was 37.2°; on 18/10, in the morning, 38.7°.

Spinal fluid, 15/10: 5/3 mononuclear cells, albumin > 30 , globulin > 3 . Throat culture, 18/10: Growth of pneumococci, Type 17.

Autopsy: Confluent hypostatic pneumonia of both lower lobes. No macroscopic signs of lymphogranulomatosis in the lungs, spleen or lymph glands.

Cultures from the heart's blood and spleen: No growth. Cultures from the spinal cord: Growth of pneumococcus Type 17.

Microscopic Examination:

Lungs: In large areas the alveoli are filled with exudate. No microscopic signs of lymphogranulomatosis in the lungs (nor in the liver or spleen).

Spinal Cord: Moderate degeneration of medullary sheaths and some increase in glia cells.

Posterior Nerve-roots: Pronounced degeneration of the medullary sheaths with fraying. In some areas the axis cylinders have undergone destruction too.

Spinal Ganglia: Considerable medullary sheath degeneration. The nerve cells contain a great deal of pigment. Gallocyanin staining reveals dust-like, bluish granules everywhere in the cytoplasm outside the heaps of pigment. Many nerve cells have under one destruction and in the capsules in which they were located, deteriorating mantle cells are seen together with leucocytes and indistinct cell lar debris.

Microscopic Diagnosis: Polyradiculitis. (Signed B. J. Wimtrup.)

Animal Experiment: After the autopsy the spinal cord and nerve-roots were placed in refrigerator (-16°).

21/10: The spinal cord is ground with sterile sand and the suspension is centrifuged lightly. A part of the supernatant fluid is injected intracerebrally into 7 mice and 4 young rabbits (weighing 1000 g). The next day the rest of the supernatant fluid is filtered through a Seitz filter, and injected intracerebrally into 2 rabbits and 8 mice. Two of the rabbits died after 5 days and autopsy showed intracranial hemorrhage. All the other inoculated animals remained well.

Patient No. 3. Girl, 7 years old.

Past history of good health.

On 26/11/40 she complained of pains in her knees, hips, shoulders and elbows. She went to school, but she fell down several times on her way to school. The pains increased during the day, and next morning she was unable to stand on her feet, and she had difficulty in using her arms.

27/11: Admitted to the hospital. Moderate rigidity of the neck and back; abdominal reflexes absent. The lower extremities are flaccid and she is unable to raise them; tendon reflexes absent, but sensation for pain normal. She is able to make small rotating movements with the right arm, and the left arm can be flexed a little; otherwise both upper extremities are diffusely paretic. Reflexes cannot be elicited; sensation for pain normal. Temperature 37.8° .

28/11: When she drinks the fluid runs out through her nose. There appears now to be an extensive hypalgesia. She has some difficulty in coughing. Slight facial paralysis on the left side, especially at the mouth; difficulty in swallowing.

Temperature now 38.4°. No dyspnoea, but the respiration is of the costal type, equal on the two sides.

30/11: Unable to cough; large amounts of foamy fluid have accumulated in the upper respiratory passage.

Auscultation of the lungs: No sign of pneumonia; scattered ronchi.

Rx. Sulfathiazole. Oxygen tent.

17 o'clock: Temperature 39.9°. Cyanosis; but the respiratory excursions of the chest are good.

19.40 o'clock: The pulse suddenly becomes imperceptible, and the patient dies a few minutes later, after about 4 days of illness.

Spinal fluid, 27/11: Pressure 120/90; albumin 10, globulin 0; mononuclear cells 1/3; sugar 58 mg %.

» » 29/11: Cells 1/3. No other examination made.

Cultures from the larynx, 30/11: Growth of pneumococci, Type 14.

Autopsy (only partial): Spinal cord together with ganglia and nerve-roots removed from the 5' cervical vertebra to the 3' lumbar.

Microscopic Examination:

In sections from the *thoracic intumescence* the posterior funiculi show groups of swollen nerve fibers with degeneration of the medullary sheaths. There is moderate oedema, but no round-cell infiltration. The oedema is pronounced round the large motor cells of the anterior horns; most of these cells are swollen and show chromatolysis, here and there with eccentric location of the nucleus. No glia proliferation.

Sections from the *lumbar part of the cord* show some groups of fibers with medullary sheath degeneration, and there seems to be a slight increase in glia cells. No inflammatory infiltration round the blood vessels within the cord.

Sections from the *nerve-roots* show marked hyperemia and, here and there, accumulations of lymphocytes. A great many of the medullary sheaths have undergone degeneration, and it is possible to demonstrate that these degenerated medullary sheaths extend into the spinal cord where they gradually turn so as to appear in cross section.

The *ganglia* show pronounced hyperemia, and the structure of the nerve cells is very indistinct. The Nissl substance presenting dusty degeneration, and there is an accumulation of pigment in the cytoplasm. A good many mononuclear cells are seen here and there interstitially.

The *leptomeninges* show here and there an accumulation of lymphocytes.

Microscopic Diagnosis: Radiculo-meningomyelitis. (Signed B. J. Vimtrup and Erna Christensen).

Animal Experiment: Immediately after the withdrawal of spinal fluid on 29/11, the fluid was injected intracerebrally into 1 rabbit and 10 mice. The rabbit died next day of intracranial hemorrhage. The mice remained well during the following months.

On autopsy the spinal cord was removed together with the appending ganglia and nerve-roots. These structures were ground with sand under sterile precautions, and the suspension filtered through a Seitz E. K. filter.

The filtrate, which was found to contain no bacteria, was injected intracerebrally into one macaco monkey about 3 cc. superficially in the parietal region and 1 cc through a deep stab in the cerebrum. The monkey remained well during the following months.

Patient No. 4. Man, 50 years old.

Past history of good health except for an attack of colicky pain in the abdomen in June 1941. In the beginning of July 1941 he had an attack of angina, and on 18/7 he had paresthesias, starting in the lumbar region and radiating down over the posterior aspects of the legs, to the toes; at the same time, he had similar sensations in the arms. There was no real pain, but the musculature was tender to pressure. The paresthesias were described partly as numbness, partly as tingling. In the following days he had a new attack of colicky pain in the abdomen under the right curvature. He was then feeling very tired and poorly, and he felt as if his tongue was swelling. His voice became hoarse and weak, and it was increasingly difficult for him to stand on his feet.

22/7: Admitted to surgical clinic, where the following findings were noted: Tongue deviating to the right; difficulty in swallowing and speaking; increasing muscular weakness; complaints of paresthesias of the arms and legs; hypalgesia of the palms and soles. No elevation of the temperature

24/7: On special neurological examination the following features were noted: Bilateral facialis paralysis; no rigidity of the neck and back; diffuse, symmetrical incomplete paralysis of the upper extremities, involving especially the dorsal flexors of the wrists; pronounced paralysis of the flexors of the knees; hypesthesia and hypalgesia of the feet and distal half of the legs; tendon reflexes moderately active.

25/7: Commencing respiratory insufficiency, on which account he was transferred to the Blegdam Hospital.

On admission here, the patient is exhausted, but not dyspneic or cyanotic. Pharyngeal reflexes cannot be elicited; voice aphonic; swallowing free; all facial muscles paretic. Movements of the eyes free.

There is now a slight rigidity of the neck and distinct rigidity of the back.

Auscultation of the lungs and heart: No abnormality.

Respiration chiefly abdominal, though with distinct function of the thoracic respiratory muscles. Hypesthesia and hypalgesia distally to the costal margins. Abdominal reflexes absent.

The arms can be elevated only with difficulty. There is marked, diffuse, symmetrical reduction in the power of all the muscle groups, especially the extensors. Extensive hypesthesia and hypalgesia. Biceps and triceps reflexes present; brachioradialis reflexes absent. The legs cannot be elevated; pronounced symmetrical reduction in the power of all the muscle

groups, but no total paralysis of any group. Extensive hypesthesia and hypalgesia. Reflexes cannot be elicited.

The patient died suddenly 8 hours after admission, on the 8th day of illness, without any sign of respiratory insufficiency.

The temperature was normal throughout the course of his illness. Blood pressure, 24/7: 140/90.

Spinal fluid, 24/7: Pressure 130/100; albumin 40; globulin 1—2; mononuclear cells 6/3.

Electrocardiography, 25/7: No abnormality.

Autopsy: No sign of pneumonia. Pronounced fibrous changes in the myocardium. Coronary arteries atheromatous, especially the anterior descending branch. Otherwise no macroscopic abnormalities except for some hyperemia round the nerve-roots and spinal ganglia, especially in the lumbar region.

Microscopic Examination:

The *cerebral cortex* shows no abnormality besides hyperemia.

The *basal ganglia of the brain* are the site of very marked hyperemia, here and there with extravasation of red blood cells. Here the nerve-cells show some effacement of the structure of the Nissl substance and indistinct cell contours.

Sections from the *lumbar intumescence* show degeneration of the medullary sheaths in the posterior funiculi, just medially to the posterior horn. The lateral fasciculi show degenerated medullary sheaths superficially. There is a rather pronounced pericellular oedema in the grey matter, especially round the nerve cells in the anterior horn. These neurones are swollen, showing chromatolysis and eccentric nuclei. No round-cell infiltration of the grey matter or elsewhere in the cord, but focal accumulation of lymphocytes in the *meninges*.

The *nerve-roots* show pronounced hyperemia; moderate medullary sheath degeneration in the posterior roots. The *spinal ganglia* from the lumbar region are markedly hyperemic, showing extravascular leucocytes as well as several mononuclear cells. Some of the nerve cells are well preserved; others show degenerative changes with large amounts of pigment in the peripheral crescent, dusty degeneration of the Nissl substance and some shrinkage, while «mantel cells» predominate towards the wide space round the cells.

Microscopic Diagnosis: Polyradiculitis or radiculo-meningomyelitis. (Signed: B. J. Vimtrup and Erna Christensen.)

Animal Experiment: On autopsy the central nervous system was removed and divided into three specimens from which emulsions were made by grinding with sand. Each of these emulsions was centrifuged lightly, and the supernatant fluid was used for injection. Filtration through a bacterial filter was omitted, so as to avoid any loss of a possibly demonstrable virus. Naturally these injection fluids were not sterile; cultures from them showed scanty growth of staphylococci and streptococci.

Specimen I, nerve-roots and spinal ganglia. On 27/7 the following animals were inoculated:

a) 1 macaco monkey, 2 cm³ intracerebrally. It remained well.

b) 7 mice, 0.03 cm³ intracerebrally. Of these mice 3 died in the following days of purulent meningitis, while the 4 remained well. On 7/8, 2 of the surviving mice were killed; their brains, which looked normal, were emulsified and injected intracerebrally into 5 mice, which all remained well.

c) 2 rabbits and 1 guinea-pig, 0.5 cm³ intracerebrally. The rabbits died in the following days of purulent meningitis; the guinea-pig presented no symptom whatever.

Specimen II, spinal cord. No take was obtained by intracerebral inoculation of 1 rabbit, 1 guinea-pig and 7 mice.

Specimen III, medulla oblongata. No take was obtained by intracerebral inoculation of 1 rabbit, 1 guinea-pig and 5 mice.

Patient No. 5. Man, 28 years old.

Past history of good health. In the beginning of September 1940 he had an «influenza»-like attack of illness with fever and headache.

7/9: Numbness and tingling sensations of the right lower extremity, with impairment of the muscular power. Next day he had similar symptoms in the right upper extremity. These symptoms got worse during the following days.

On the night of 9/9, increasing weakness and paresthesias of the left lower extremities, together with beginning symptoms in the left upper extremities.

9/9: Admitted to the Blegdam Hospital. On admission no particular exhaustion, but some rigidity of the neck and back. Kernig's sign positive. During the following day and night the pareses developed into a symmetrical, incomplete tetraplegia with lowered sensibility but without definite absence of reflexes. No cranial nerve paresis. Unable to void.

11/9: Increasingly exhausted. Now difficulty in breathing has appeared too, and the patient is drowsy and cyanotic, unable to expectorate on coughing. Auscultation now reveals signs of pneumonia.

Rx. Sulfathiazole.

Placed in respirator.

12/9: Exitus in the respirator, after 7 days of illness.

The first two days in the hospital the temperature kept between 37° and 38°; after that, it rose.

Spinal fluid, 9/9: Clear; albumin 10, globulin 2.

16/3: Mononuclear cells; sugar 42 mg %.

11/9: Clear; pressure 180/140; albumin 30, globulin 3, mononuclear cells 10/3; sugar 44 mg %.

Culture from the larynx, 11/9: Growth of pneumococci, Type 19. White blood count, 11/9: 20300, with 85 % neutrophil leucocytes.

Autopsy (Dr. B. J. Vimtrup): The central nervous system is removed together with ganglia. No macroscopic abnormality besides hyperemia of the leptomeninges. In the right lung, the middle and lower lobes show confluent areas of fibrinous bronchopneumonia. In a specimen from this process the presence of pneumococci, Type 19, is demonstrated.

In the heart the left ventricle shows a couple of streaky extravasations of blood beneath the endocardium, corresponding to the bundle of His-Tawara.

Microscopic Examination:

Sections from the *cervical spinal cord* show accumulation of lymphocytes round the *nerve-roots*, in the perineurium and endoneurium. Correspondingly, the nerve fibres in the anterior and lateral fasciculi are swollen and staining poorly. Kulschitsky stain shows medullary sheath degeneration.

The *leptomeninges* show round-cell infiltration that can be followed into the anterior medial fissure and in round the blood vessels in the central canal, where the blood vessels are surrounded by cuff-like infiltrations. On the anterior surface of the *medulla oblongata*, at the level of the respiratory center, the leptomeninges are likewise infiltrated slightly with round-cells, here and there, whereas the nervous tissue itself is not involved. Sections from the *thoracic spinal cord* present the same features.

Microscopic Diagnosis: Radiculo-meningomyelitis. (Signed: B. J. Vimtrup.)

Animal Experiment: The spinal fluid obtained on 9/9 was used half-an-hour after its evacuation for intracerebral inoculation of 1 rabbit (I), which was given a dose of 1 cm³, and 10 mice that were given an intracerebral injection of 0.03—0.05 cm³. Of the mice, two died of this operation.

On 19/9, rabbit I, which presented no symptoms whatever, was killed. The brain was removed under sterile precautions, emulsified and filtered through a Seitz filter. Rabbit II was given an intracerebral injection of 1 cm³ of this filtrate.

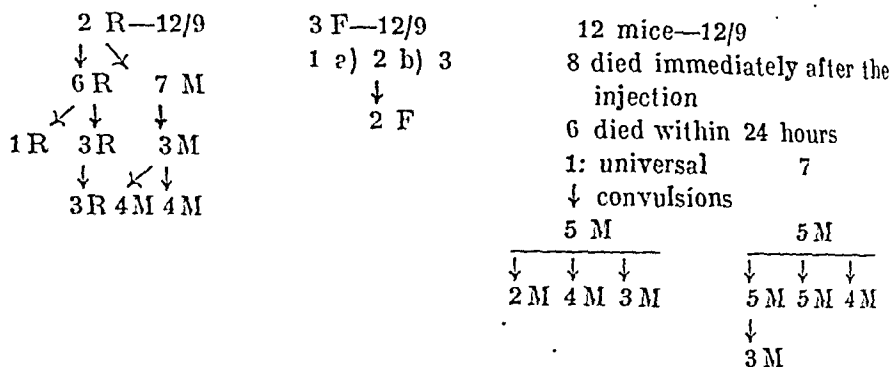
On 1/10 and 14/10 the same experimental procedure was repeated (Rabbits III and IV). These animals all remained well throughout the observation period (in the case of Rabbit IV it lasted a couple of months).

On 19/9: Of the surviving 8 mice which had been inoculated on 9/9 — they were all «well» at this point of time — 4 were killed (the remaining 4 mice kept being symptom-free). The brains were removed under sterile precautions and emulsified. Then 8 mice were inoculated intracerebrally with 0.05 cm³ of the emulsion. On 1/10 and 14/10 the same procedure was repeated on two new groups of mice, all of which remained well.

On autopsy, on 12/9 — the day the patient died — the entire spinal cord was removed together with ganglia from the medulla oblongata to the cauda, and ground with sand and sterile salt solution. Seitz filtration was attempted but had to be given up. The emulsion was centrifuged lightly and, on the same day, inoculated into 22 mice, 2 rabbits and 3 ferrets. The

inoculations were carried further as shown in the diagram below. In no instance did this treatment result in symptoms that could be interpreted as «takes».

Emulsion of Nerve Tissue from Patient No. 5 employed for Intracerebral Inoculation.



16/9

Glycerine extract of nervous tissue injected intracerebrally into 2 rabbits

R = rabbit, F = ferret, M = mouse.

a) transitory functional impairment of the left forepaw and right hind paw; well on the 11' day; surviving 11 months.

b) after a few days, functional impairment of the right forepaw and right hind leg, with «wobbly» gait. Killed on the 8' day. Emulsion of the brain injected intracerebrally into two other ferrets that remained quite free from symptoms for 11 months.

So the outcome of our experiments on demonstration of a virus, for which a total of 201 animals were employed — 157 mice, 34 rabbits, 5 ferrets, 3 guinea-pigs and 2 macaco monkeys turned out completely negative. This outcome appears to lend some support to the view concerning the etiology of polyradiculitis that has been advocated particularly in recent years, namely: that acute polyradiculitis is not due to an infectious agent.

In his recent monograph, Pette (1942) has enumerated various factors going against an infectious etiology:

1. The deterioration of nerve fibers characteristic of acute polyradiculitis is not seen in other virus infections of the central nervous system — poliomyelitis, epidemic encephalitis. This is quite true, but it should be kept in mind that so far it has not been possible with certainty to establish the virus characteristic of the so-called epidemic encephalitis (v. Economo).

2. In comparison to the findings in the virus diseases mentioned here, the injury to the nerve cells in acute polyradiculitis is minimal.

3. In polyradiculitis the inflammatory reaction is slight.

4. The symmetrical distribution of the pareses in polyradiculitis does not speak in favor of an infectious origin and forms a striking contrast to the findings in a greater majority of poliomyelitis patients.

5. The not infrequent exacerbations encountered in cases of polyradiculitis are never seen in the aforementioned virus infections of the central nervous system.

Finally, it is mentioned that no virus has been demonstrated in the animal experiments with inoculation performed so far.

Hence the experiments of this kind that have been reported hitherto are very few and, as far as we know, comprise merely a few animals, the outcome of our experiments will be entitled to some interest and be of some significance, as it goes against the hypothesis that acute polyradiculitis (radiculo-meningomyelitis) of the Landry type is of infectious origin.

We quite realize, however, that our experimental results do not go decisively against such an assumption. For one thing they are too few in number — and this applies in particular to the experiments on monkeys. In the next place, it is conceivable that in the animals here employed it requires the interaction of two factors to obtain a «take» — the virus in question and a state of insufficiency of some sort or other, possibly a «hypovitaminosis».

Whether the disease may be due to an allergic reaction in the central nervous system — a view that is advocated strongly by Pette — will have to remain an open question, as the histological examination of the nervous system of the present patients gives no information about this possibility.

Summary.

An account is given of 5 cases of typical acute polyradiculitis (radiculo-meningomyelitis), 4 of which terminated fatally. A detailed abstract of the case histories is given together with a description of the autopsy findings and the histological examination of the central nervous system.

Spinal fluid from these patients or emulsions prepared from various parts of the central nervous system are employed for intracerebral inoculation of 201 animals — 157 mice, 34 rabbits, 5 ferrets, 3 guinea-pigs and 2 macaco monkeys — without any instance of successful transmission of this disease.

In conclusion, a brief mention is made of other factors suggesting that acute polyradiculitis is not of infectious origin.

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Determination of Carbon Monoxide in the Blood.

By

ESTHER AMMUNDSEN and AAGE GRUT.

(Submitted for publication May 3, 1943).

With the recent increased use of apparatuses (producer-gas sets, charcoal stoves) which produce carbon monoxide (CO) there is a growing demand for a method whereby the content of carbon-monoxide hæmoglobin can be determined with rapidity and with sufficient certainty.

In the daily clinic, too, it is of importance when estimating the prognosis and instituting treatment. It is of great importance to know whether or not the excretion of COHb proceeds slowly, and whether e. g. deranged sensorium or insufficient circulation is due to a still existing intoxication or the consequences of such intoxication, and this can be found out only by determining the COHb.

This cannot be done by means of the methods employed in forensic medicine, which are qualitative and may be employed for the purpose of ascertaining the presence of CO-poisoning, but they are useless for determining the grade.

For many years we have had exact quantitative methods, for example van Slyke's and Sendroy's gasometric analysis (1) (2), but they require some practice in gasometric technique, for which reason they are not much used in the clinic.

When in the beginning of 1940 Norwegian (3) and Swedish (4) methods appeared, for which it was claimed that they combined accuracy with simplicity, we found it essential to test them.

We have therefore tested blood samples containing various quantities of CO by means of van Slyke's, Wennesland's and Wolff's methods.¹

Van Slyke and Neill's method (1), which is the earliest, is carried out in van Slyke's gasometric apparatus and consists in expelling all the gases of the blood by shaking the blood in a vacuum in an acid solution of potassium ferrieyanide. Oxygen and carbon dioxide are absorbed and the pressure of the remaining carbon monoxide + nitrogen is measured, whereafter a constant is deducted for the nitrogen. The method was carried out as described by van Slyke and Neill.

Wennesland's method (3) is based upon the fact that carbon monoxide reduces palladium chloride to free palladium, which lies like a thin layer on the palladium-chloride solution.

To make the analysis two Erlenmeyer flasks are connected by a short length of wide rubber tubing. A known quantity of palladium chloride is placed in one, the blood in the other. The haemoglobin is converted by sulphuric acid, whereby oxygen and carbon monoxide are expelled. The sample stands for 18 hours or is placed in a rotating apparatus for 4 hours, whereafter the remaining quantity of palladium chloride is determined. (In the present work the analyses were made by allowing the samples to stand for 18 hours.)

For details the reader is referred to the original work.

Wennesland's technique suffers from a defect which, at the higher concentrations, will presumably have the effect that the results obtained are too low, for he adds the sulphuric acid before the two flasks are connected, thus providing a possibility for some of the carbon monoxide to escape. The relative importance of this source of error may presumably be reduced by measuring the blood under water and thereafter allowing the sulphuric acid to run down the side of the flask, carefully avoiding any shaking, before the flasks are connected, whereafter they should be shaken vigorously.

For the purpose of trying to avoid this error altogether we tried measuring the sulphuric acid in dwarf tubes placed in the flask and shaken out only when the system was sealed. This method, however,

¹ Tests with van Slyke's and Wennesland's methods were made by Esther Ammundsen in the Rigshospital's Department B, and we thank Professor E. Warburg, M. D. for kind permission to do so. Those with Wolff's method were made by Aage Grut in the laboratory of the Factory Directorate.

had the drawback that air bubbles sometimes formed inside the dwarf tubes, so that not all the air came into contact with the palladium-chloride solution.

Table 1.

Sample No.	Wennesland				Van Slyke & Neill	
	With dwarf tubes		Without dwarf tubes			
	Vol. %	Hb %	Vol. %	Hb %	Vol. %	Hb %
1	6 05	32 6	6 03	32 5	6 58	35.5
	6 09	32.9	6.34	34.2	6.46	34 9
	5.71	30 8	6.41	34 6		
2	5.17	27.9	4 88	26.4		
	4.31	23 3 ¹	5.39	29.1		
	3.91	21.1 ¹	5.62	30.3		

The Hb % calculated according to Haldane's standard.

Table 1 shows the values obtained with and without the dwarf tubes and it will be seen that no better results are arrived at with the said modification of the method, but that in fact — as in the case of the samples marked ¹ — one often achieves decidedly lower values, presumably because part of the carbon monoxide is confined in the dwarf tubes.

Consequently, we elected to employ the method as described by Wennesland, great care being observed not to mix sulphuric acid and blood before the system is closed — as the colour of the blood changes from red to brown when the haemoglobin oxydises, this is relatively easy to control — and the degree of accuracy attained is presumably high enough for clinical purposes. If the method is to be employed for carbon-monoxide capacity determinations or for the determination of large amounts of carbon monoxide in the blood, it will presumably be necessary to use a specially designed apparatus to permit of the addition of sulphuric acid after the flasks are connected, with no chance of enclosed spaces within the system.

The results we obtained in comparison with van Slyke and Neill's method cannot in accuracy be measured against those obtained by Wennesland by comparing with gasometric methods [Sendroy and

¹ See text.

Liu (2)]. The reasons have not been cleared up, but the results are doubtless sufficiently accurate for clinical use.

Wolff's method (4) in principle is based on a fact originally observed by Hartridge (6), that oxyhaemoglobin coagulates more readily in heat than does CO-Hb.

Wolff tested various temperatures and hydrogen-ion concentrations and eventually selected 55° and P_H : 5.0—5.3 as the most suitable. The method is described as follows:

Dilute 1 ml. blood with 4 ml. water. To 1 ml. of this 20 per cent. solution add 4 ml. buffer solution. Allow the mixture to stand exactly five minutes in a water-bath at 55°. Centrifuge after immediate cooling and compare the liquid above the precipitate with two standard liquids, one intended for daylight, the other for artificial light. The standard artificial-light solutions are prepared from cobalt nitrate, of which a $\frac{m}{1}$ solution is stated to correspond to 50 % COHb, a $\frac{m}{2}$ solution to 25 % COHb, and so on.

The daylight standard is prepared by diluting the aforesaid $\frac{m}{1}$ cobalt nitrate solution with $\frac{m}{10}$ uranyl acetate instead of water, thus giving a more yellowish solution. As regards cobalt nitrate a $\frac{m}{2}$ solution corresponds to 50 % COHb, a $\frac{m}{4}$ to 25 % COHb, and so on.

In certain respects we modified Wolff's technique; the two initial pipette transfers are replaced by one, for we add 0.2 ml. citrated blood direct to 0.8 ml. H_2O . By this means we avoid a manipulation that might cause the loss of some CO, and in addition one can use ear blood direct. Furthermore the samples were compared with the daylight standard in both daylight and artificial light, and with artificial-light standard in artificial light, and the average of the values found were employed. This procedure was adopted because the daylight standard, even in artificial light, gives better colour agreement than the artificial-light standard at the low COHb percentages.

However, it often happens that at one of the readings the colours agree so badly that one can only use the other two. On the whole these colour concordances are the Achilles'heel of the method, as

the personal factor is unavoidable when the colours do not agree completely. At any rate, one cannot manage with one standard. The source of artificial light is a daylight bulb, and as a background a sheet of white paper illuminated by direct daylight or by daylight bulb, this arrangement presumably being one that can be reproduced unchanged from place to place, whereas tubes held up to an ordinary electric bulb would have a most heterogeneous light source.

Finally, we omitted Wolff's addition of sodium hyposulphite to the liquid before reading. It is true that this addition makes the colour stronger, but at the same time it acquires a bluish tint which does not agree with the standard colour.

By means of our procedure the artificial-light standard corresponded to the daylight standard, so that artificial-light standard with $\frac{m}{2}$ cobalt nitrate like the daylight standard corresponds to 50 % COhb, $\frac{m}{4}$ to 25 %, and so on.

As regards the various sources of error contained in the method we have examined the question of how closely the various experimental conditions (temperature, heating time, buffer P_H) should be adhered to, and of whether the theoretically necessary manipulation under paraffin oil makes any difference to the result.

1. Effect of Water-bath Temperature.

Table 2 shows the effects of varying temperature on blood samples with various COhb contents.

Table 2.

	53°	54°	55°	55.5°	57°
COhb %	100		88		78
	63	48	44	46	25
		30	31	34	
		20	19	14	
		8	9	9	
		9	6		
		3	0		

It will be seen that the difference between the values on heating to $55^\circ \pm 1^\circ$ is insignificant, whereas there is a considerable difference if the variation is $\pm 2^\circ$. The 55° should therefore be carefully adhered to.

2. Effects of Heating Time.

The samples were heated for 0—15 minutes, but otherwise treated in the usual manner. After centrifuging the liquid above the precipitate is of course of a deeper colour in the unheated samples than in the heated ones, as the former contain both oxy- and carbon-monoxide haemoglobin. The colours were compared with the standard and the values arrived at placed in Table 3.

Accordingly, only those values that correspond to five minutes heating time indicate the true COHb content.

Arranged in a coordinate system we get the following curve (Fig. 1) for the *heat precipitation of carbon monoxide + oxy-haemoglobin*:

Heat precipitation of COHb + O₂Hb.

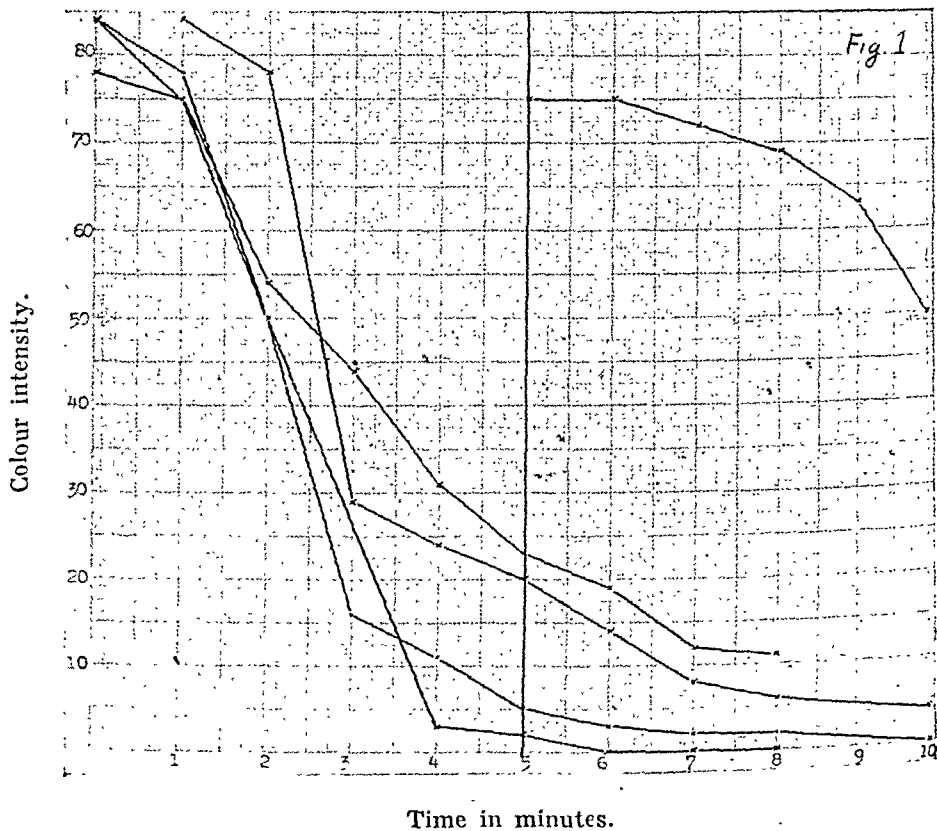


Table 3.

Heating Time in minutes.

	0	1	2	3	4	5	6	7	8	9	10	15
Colour intensity						75	75	72	69	63	50	25
78		75	54	44	31	23	19	12	11			
		84	78	29	24	20	14	8	6		4	
84		78	50	16	11	5	3	2	2		0	
84		75	50		3	2	0	0	0			

The values of the ordination (colour intensity) are obtained by comparing the samples with the standards in the ordinary way. Of course only the 5 minute ordination (Colour intensity of samples heated for 5 minutes) represents the carbon monoxide content of the sample. At the high COHb percentages there is — in conformity with the theoretical presupposition of the method — only little precipitation from heating for six to seven minutes, whereas 60 to 80 per cent. of the oxyhaemoglobin is precipitated after three minutes, as the other curves show. On the other hand, all the oxyhaemoglobin does not seem to have been precipitated after five minutes, as with the medium COHb contents there is a fall that continuously passes the five-minute ordination. This can scarcely mean other than that after five minutes one actually reads COHb + part of the oxyhaemoglobin. This is also to be seen from the fact that there is a change of colour if sodium hydrosulphite is added to the solution after the five minutes' heating. Thus theoretically we must expect unduly high values from the method when the carbon monoxide haemoglobin percentages are low or medium. It is evident from fig. 1 that the heating time of the samples must be exactly 5 minutes.

3. Buffer P_H .

Wolff states that his buffer has a P_H of 5.0—5.1, which corresponds to the calculated value. For the buffers we used we found values of 5.15—5.20 with the potentiometer, and with this variation we found no difference in the COHb percentages with variations from 1 to 50 % COHb.

The Methods Compared.

The blood of the samples came from people with carbon monoxide poisoning (motor-drivers using producer-gas sets, workers at repair shops for producer-gas sets, and a few cases of acute, more severe poisoning) and from normal blood artificially saturated with CO. When the latter is to be used for the preparation of samples with a low COHb content, a weak carbon-monoxide dilution must be employed in order to avoid getting so much physically combined CO that it binds the haemoglobin in the dilution blood. We therefore employed a mixture of 98 % air + 2 % CO. Furthermore, for van Slyke's method we used pure CO (not illuminating gas), and no volatile matter (oktylalcohol) was added to the blood. The sample was tested at once with Wolff's method — the same afternoon, at the latest next day with the other two methods — and finally again with Wolff's method. (Table 4, pag. 10).

Finally, in seven analyses there were traces with Wennesland's methods, and 0.1, 1, 2, 2, 3 and 5 % respectively with Wolff's method. In 18 analyses all three methods gave 0.

The results are summarized in Table 5.

Table 5.

COHb %	Maximum deviations			Average numerical deviations		
	v. S.-Wenn.	Wenn.-Wo.	v. S.-Wo.	v. S.-Wenn.	Wenn.-Wo.	v. S.-Wo.
0—10	2 (13)	4 (35)	3 (11)	0.6	0.8	1.6
11—30	4 (4)	5 (7)	4 (4)	3.0	2.1	2.5
31—50	11 (5)	11 (9)	2 (4)	7.6	5.8	1.3
51	5 (3)	ca. 9 (2)	11 (4)	3		8

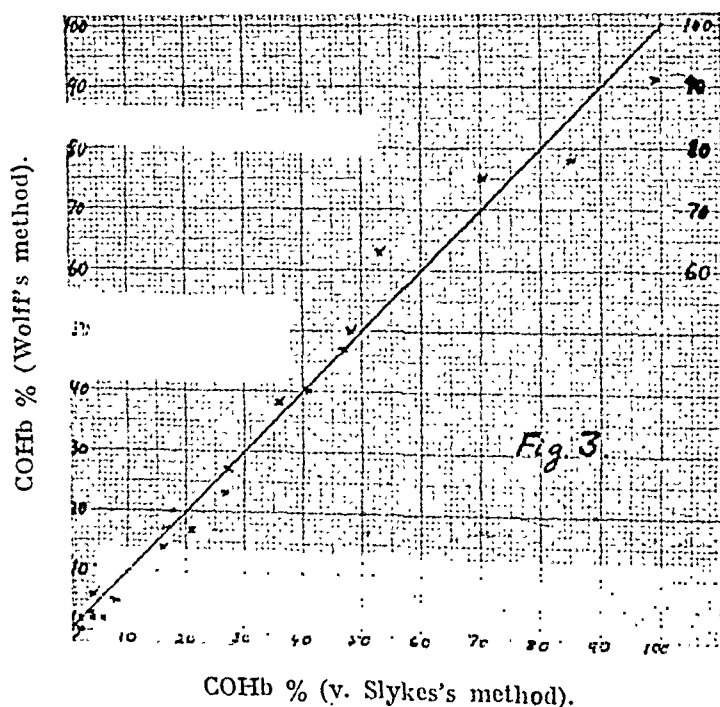
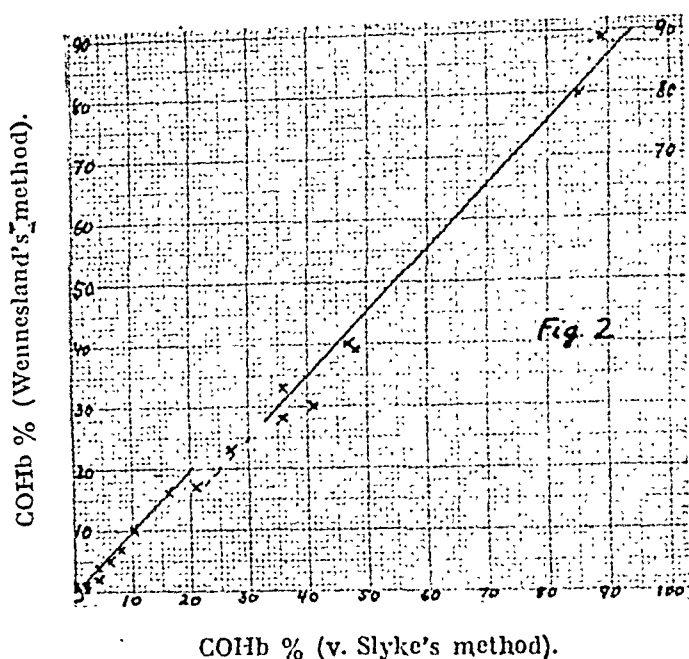
In Table 5 the figures in brackets represent the number of analyses by means of van Slyke's (v. S.), Wennesland's (Wenn.) and Wolff's (Wo.) methods. The deviations are shown numerically in COHb %.

If the values are arranged in a co-ordinate system (figs. 2 and 3) it will be seen that those arrived at by van Slyke's and Wolff's methods and by Wennesland's method with values under 20 % COHb agree fairly well, whereas in the case of Wennesland's

Table 4.

van Slyke	Wennesland	Wolff
99	106	91
90	89	
85	80	
85		78
70		75
	66	50
53		63
48	39	50
47	40	47
41	30	40
36	28	38
36	33	
	33	32
	33	31
	31	36
	31	30
	30	25
	29	31
27	23	27
27	23	23
21	17	17
16	16	14
	12	10
10	10	
	9	10
	9	6
	8	6
8	7	5
	8	8
	6	8
	5	5
	5	2
6		3
5		2
4	4	3
4		6
4	2	1
	2	2
2	1	0
2	0	2
	2	2
0	1	2
0		1
	0	1
	0	2
	0	2
	0	2

method with values of over 20 % COHb about 5 % must be added to the figures in order to obtain the same values as with the van Slyke method.



The conclusion arrived at from the investigation is that the methode of both Wennesland and Wolff in the aforesaid modification are useful for clinical purposes. Wennesland's method has the drawback that it takes a long time, but on the other hand there is no personal factor in the result. Wolff's method is rapid, but the conditions must be observed very closely, and at the high concentrations the colour agreement is not good. Both methods can be employed in any laboratory. For examinations requiring great accuracy the gasometric analyses must still be employed.

Summary.

Blood samples with varying contents of carbon monoxide haemoglobin have been tested by three methods. 1) van Slyke & Neill's gasometric, 2) Wennesland's titrimetric, 3) Wolff's colorimetric. The latter method is modified somewhat. At values of under 20 % carbon monoxide haemoglobin there is good agreement; at higher values the figures obtained with Wennesland's method are about 5 % too low.

Reference is made to the advantages and drawbacks of the methods.

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Direktor: Professor Dr med. G. Bergmark).

Morbus Schaumann—Morbus Basedow.

(Ein Fall von Morbus Schaumann mit Lokalisation u. a. in
Glandula thyreoidea mit Hyperthyreose.)

Von

STEN OLDBERG.

(Bei der Redaktion am 10. Juni 1943 eingegangen.)

Die Krankheit, welche wir in Schweden nunmehr Morbus Schaumann (M. S.) nennen, hat viele Namen gehabt, deren Geschichte nicht ohne Interesse ist. »Names are good servants but bad masters». Diese Sentenz wurde von Jonathan Hutchinson geprägt und kann gut für die Krankheitsform gelten, die er als erster von allen beschrieb. Selbst benannte er neue Syndrome oder Krankheiten nach dem Patienten, bei welchem sie beobachtet wurden und brachte dadurch kaum Ordnung in die Nomenklatur. Im Jahre 1869 beschrieb Hutchinson eine Krankheit, die er nach ebenerwähntem Verfahren als »Mortimers Malady» bezeichnete. Es war ein Patient mit sonderbaren Hautveränderungen auf der Vorderseite der Beine, an den Fingern und dem einen Unterarm. Die Effloreszenzen waren blaurot, erhöht, unregelmässig mit scharfen Kanten samt glatter Fläche und weder empfindlich noch schmerzhaft. Ausserdem zeigte ein Finger des Patienten eine feste ödematöse Geschwulst. Verf. bemerkte, dass der Zustand noch nach einem Jahre unverändert war, trotz verschiedenen therapeutischen Behandlungsmethoden. Im Sommer 1869 besuchte Hutchinson das damalige Kristiania und bekam dort einen Fall zu sehen, der mit seinem eigenen gut übereinstimmte. » — — — Professor Boeck told

me that it was the only example of its kind that he had ever seen». Wie bekannt, ist der Name Boeck mit diesem Krankheitszustand fest verbunden. Die Ehre kommt jedoch nicht dem ebenerwähnten (Carl William) Boeck zu, sondern seinem Neffen und Nachfolger auf den Lehrstuhl, Caesar Boeck. Die Publikation des Letzteren erschien aber erst 1899. Zuvor hatte Besnier (1889) in guter Übereinstimmung mit Hutchinson seinen Lupus pernio beschrieben. Die Histopathologie wurde zuerst von Boeck geschildert, der die Krankheit »multiples, benignes Sarkoid« nannte. Derselbe Verfasser wies darauf hin, dass ausser der Haut ebenso Schleimhäute und Lymphdrüsen ergriffen werden können. Es zeigte sich auch bald, dass Besnier's Lupus pernio und Boeck's Sarkoid histologisch identische Krankheiten waren. Der nächste beachtenswerte Fortschritt wurde von Röntgenologen gemacht. Kreibich (1904) sowie Rieder (1910) fanden bei Lupus pernio und Morosoff (1908) bei einem Fall von Boeck's Sarkoid charakteristische Skelettveränderungen. In den Phalangen, gewöhnlich an der Grenze zwischen Epiphyse und Diaphyse, entstehen bläschenförmige Verdünnungen und Lochbildungen, »Billettlöcher«. Jüngling hat später diese Skelettveränderungen eingehend studiert und ihnen den Namen *Ostitis tuberculosa multiplex cystoides* gegeben.

Schaumann (1914) wies zuerst auf die allgemeine Ausbreitungstendenz der Krankheit hin. Dieser Verfasser betonte, dass die Hautveränderungen nicht obligat, sondern nur als ein zuweilen auftretendes Teilsymptom aufzufassen seien (*Lupus pernio sine lupo*). Von übrigen Organen, die ergriffen werden können, erwähnte Schaumann das ganze lymphatische System, inkl. Milz, Leber und Lungen. Verf. konstatierte offenbare Ähnlichkeiten mit einer anderen Systemkrankheit mit spezifischem Granulationsgewebe, *Lymphogranulomatosis maligna* (Hodgkin). Der wichtigste Unterschied war die Prognose, weshalb Schaumann die Bezeichnung *Lymphogranulomatosis benigna* für die neue Systemkrankheit vorschlug. Diese Terminologie entging jedoch nicht der Kritik und auf dem Dermatologkongress in Strassburg 1934 einigte man sich über den Namen »*Maladie de Besnier-Boeck*«. Dessen ungeachtet änderte man wiederum im folgenden Jahre auf einem internationalen Kongress in Budapest diese Benennung zu *Morbus Schaumann*. In vorliegender Arbeit wird die Bezeichnung *M. S.* angewandt.

1929 konnten Mylius und Schürmann die einheitliche pathologisch-anatomische Unterlage dieser Krankheit angeben, die sie »universelle, sklerosierende, tuberkulöse, grosszellige Hyperplasie« nannten. Unabhängig von diesen Verfassern beschrieb Hantschmann (1930) einige ähnliche Fälle von »torpider Form disseminierter Tuberkulose«. Die Krankheit erregte in späteren Jahren grosses Interesse von verschiedenen Seiten. Zahlreiche kasuistische Beiträge wurden geliefert und man konnte sie in fast allen Geweben und Organen des Körpers nachweisen; in Haut, Skelett, Knochenmark, Muskulatur, Lymphdrüsen, Milz, Leber, Urogenitalapparat und Lungen. Rechnet man, wie einige Autoren (Waldenström, With u. a.) aus berechtigten Gründen getan haben, auch Febris uveo-parotidea zu M. S., kann man die Kasuistik erweitern mit Fällen, welche die Augen, die Speichel- sowie Tränendrüsen und das zentrale Nervensystem betreffen. Auch in den endokrinen Drüsen hat man M. S.-Veränderungen gefunden, jedoch so selten, dass schon aus diesem Grunde der vorliegende Fall erwähnenswert ist.

Mehrere Fälle von M. S. enthalten Angaben über Polyurie (Heerfort, Jersild, Levin, Lesne-Launay-See u. a.). Gewöhnlich wurde dieses Symptom als Diabetes insipidus aufgefasst, durch spezifisches Granulationsgewebe in der Hypophyse oder im Hypothalamus verursacht. Tillgren hat einen Fall von Lupus pernio und Ostitis tuberculosa multiplex cystoides mit Polyurie bis zu 6 Liter innerhalb 24 Stunden veröffentlicht. Bei der Sektion konnten typische Epiteloidzellherde ohne Nekrose im Mittellappen der Hypophyse konstatiert werden. Diese Epitheloidzellhaufen waren wie sonst im M. S.-Gewebe mehr oder weniger durch Bindegewebe ersetzt. In einem von Schaumann's Fällen fand Wahlgren ähnliche Veränderungen im Hinterlappen der Hypophyse. Auch dieser Patient hatte Symptome von Diabetes insipidus gezeigt. Lundholm beobachtete einen Fall von M. S., der nach einer monocytären Meningitis während des floriden Stadiums der Krankheit das Bild von Simmond's Kachexie darbot. Letzterer Symptomkomplex blieb bestehen, trotzdem die Veränderungen in den Lungen und Lymphdrüsen zurückgingen. Nach Verabfolgung von Hypophysenpräparat trat fast vollständige Restitution in weniger als einem Monat ein. Da man gefunden hat, dass die intrakraniellen Veränderungen bei M. S., besonders die Meningitis, sich hauptsächlich basal um den Infundibulum lokalisieren, scheint die in Lund-

holm's Fall konstatierte Meningitis genügend, um das beschriebene Krankheitsbild hervorzurufen. Es ist möglich, dass der Mechanismus in einem Teil der Polyuriefälle derselbe ist. Es dürfte sonst schwierig sein, die Affinität zwischen dem M. S.-Granulom und der Hypophyse zu erklären. Die Patienten, bei denen die Speicheldrüsen im Prozess engagiert sind, leiden oft an ausgesprochener Trockenheit im Munde, der eine gerötete trockene Schleimhaut aufweist. Es ist betont worden, dass aus diesem Anlass die Polyurie ihren Grund im Polydipsie haben kann.

Ustvedt hat in diesem Zusammenhang einen Fall von Interesse veröffentlicht. Er betraf eine 60-jährige Frau, die im März 1929 mit den Symptomen eines Myxödems in das Krankenhaus eingeliefert wurde. Durch Thyreoidamedikation trat Verbesserung ein. Im Mai 1937 erschienen kleine rote Flecken und Knoten an den Beinen, welche vom Dermatologen als »miliare Form von Boeck's Sarkoid« diagnostiziert wurden. Nach Probeexcision der Haut fand man typisches Granulomgewebe. Im Januar 1938 entstand empfindliche Schwellung der Parotis- sowie Submandibulardrüsen auf beiden Seiten und der Tränendrüse auf der linken Seite. Der Augenarzt konstatierte Conjunctivitis sicca, wahrscheinlich sekundär durch die herabgesetzte Tränensekretion verursacht. Pirquet-Reaktion war wiederholte Male schwach positiv. Röntgen der Lungen im Februari 1938: »verkalkter Primärkomplex, rechtsseitige Hilusadenitis und ausserdem kleinfleckige Verdichtungen in den unteren Teilen des Lungenfeldes, an Mylius-Schürmann's Krankheit erinnernd«. Röntgen der Hände und Füße zeigte: »Aufhellungen im rechten Radius wie bei Jüngling's Ostitis cystoides«. Ustvedt's Fall ist eine schöne Illustration zur Vielfältigkeit in der Nomenklatur und Klinik dieser Krankheit. Von besonderem Interesse ist, dass der Patient von Anfang an das Bild eines Myxödems darbot. Ustvedt vermutet in diesem Falle die Möglichkeit von »Sarkoid-foci« in der Thyreidea. Probeexcision wurde nicht gemacht. Ein ähnlicher Fall ist von Stallard-Tait geschildert worden. Bokström hat bei einer 49-jährigen Frau M. S. mit gleichzeitiger Struma und thyreotoxischen Symptomen beobachtet. Er hält das Vorkommen von M. S.-Gewebe in Glandula thyreidea für möglich, doch fehlen Beweise. Im Jahre 1938 schilderten Spencer-Warren einen Fall von M. S., der bei Sektion typisches Granulomgewebe u. a. in Glandula thyreidea zeigte. Klinisch konnten keine

Thyreoidaestörungen konstatiert werden. Die Verfasser machen darauf aufmerksam, dass dies der erste Fall ist, bei dem durch Sektion eine solche Veränderung nachgewiesen werden konnte. Ich habe in der Literatur keinen Fall finden können, bei dem intra vitam konstatiert werden konnte, dass Glandula thyreoidea vom M. S.-Prozess angegriffen war. Überhaupt ist somit die Lokalisation von M. S. in den endokrinen Drüsen wenig bekannt und die Symptome sind demgemäss unklar. Wie aus den meisten relatierten Fällen hervorgeht und wie man nach der Art der pathologisch-anatomischen Veränderungen erwarten kann, scheint eine Hypofunktion die Folge einer derartigen Komplikation zu sein.

Im Oktober 1941 wurde an der hiesigen medizinischen Abteilung ein Fall von M. S. gepflegt, der von mehreren Gesichtspunkten aus interessiert. Es handelt sich um eine 54-jährige Frau, die früher im grossen und ganzen stets gesund war. Seit wenigstens 15 Jahren litt sie an Augenbeschwerden in Form von brennendem Gefühl und Rötung der Conjunctivae, die mit Borsäure und Zinktropfen behandelt wurden. Im Frühling 1941 beobachtete Pat. eine Struma, die seitdem in der Hauptsache unverändert war. Von dieser Zeit an litt Pat. an Schwitzungen, Hitzegefühl im ganzen Körper, fühlte sich müde und wurde sehr mager. Sie bemerkte auch, dass »die oberen Augenlider über den Augen hingen«. Seit August 1941 konnte sie über beiden Augen ein Paar feste Resistenzen unter dem oberen Orbitalrand fühlen. Aus diesem Anlass besuchte Pat. die hiesige Augenpoliklinik. Dort wurde eine leichte chronische Conjunctivitis sowie doppelseitige Dacryoadenitis konstatiert. Man fand keine Zeichen von Iritis, auch nicht von Keratoconjunctivitis sicca. Auf Grund der chronischen, bilateralen Dacryoadenitis vermutete man Systemkrankheit, weshalb Pat. zur medizinischen Abteilung überführt wurde.

Aus dem Status: Allgemeinzustand ziemlich gut. Pat. wirkt etwas ängstlich und labil. Haut geschmeidig. Feinwogiger Fingertremor, leichter Exophthalmus, Tachycardie (ungefähr 90 per Min.). An der Stelle für die Tränendrüsen buchten feste, lobierte Resistenzen hervor. Glandula submaxillaris sin. möglicherweise etwa fester als normal. Lymphdrüsen pathologisch nicht vergrössert. Thyreoidea mässig diffus vergrössert mit ziemlich weicher Konsistenz; Isthmus von einer ungefähr haselnussgrossen festeren Partie eingenommen, Adenom? Physikalische Untersuchung von Herz und Lungen ohne

Anmerkung. Röntgenuntersuchung der Lungen: »In beiden Lungenfeldern eine mässige kleinfleckige Zeichnung, Emphysem. Verkalkter Primärkomplex auf der linken Seite. Hilusschatten vergrössert, besonders rechts. Art des Prozesses ungewiss». Vom Bauch nichts besonderes. Blutuntersuchung im grossen und ganzen normale Verhältnisse. Weisse Blutkörperchen ca. 5000. W. R. negativ. Sternalpunktion nichts pathologisches. Pirquet-Reaktion positiv. Grundumsatz: +45, +46, +47 %. Mit Verdacht auf M. S. wurde

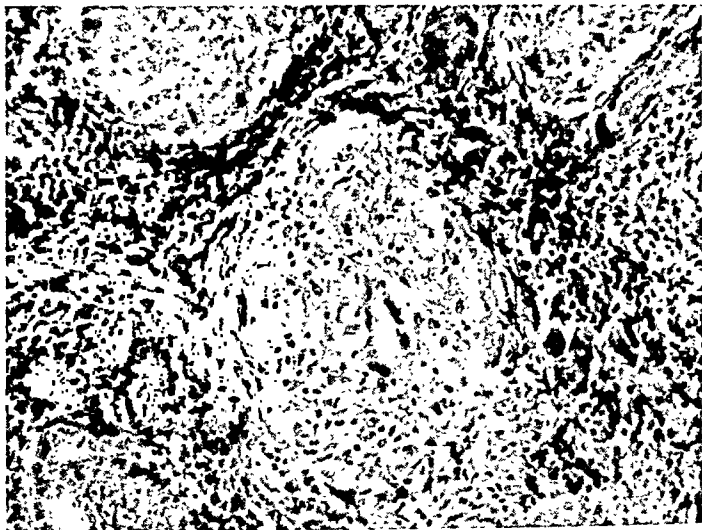


Fig. 1. Glandula lacrimalis sin.: Epitheloidzellstuberkeln mit Riesenzellen ohne deutliche käsige Nekrose.

Probeexcision der Glandula lacrimales sin. gemacht. P. A. D. (Gellerstedt): »Atypische Tbc. Die Probe besteht aus einem Tränendrüsen-
teil, der von zahlreichen Epitheloidzelltuberkeln durchsetzt ist mit nur einzelnen Riesenzellen und ohne deutliche käsige Nekrose. Mässig fibröse Induration des Drüsengewebes, etwas Indurationstendenz auch bei einem Teil der Tuberkeln. Dürfte sich dem nähern, was man in den Organen bei der sog. Morbus Schaumann findet, jedoch sind in den Riesenzellen keine Fremdkörper beobachtet worden» (Fig. 1). Das Röntgenbild des Hand- und Fuss skelettes zeigte keine typischen Veränderungen. Auf Grund der bekannten Ausbreitungstendenz von M. S. wurde auch eine Probeexcision der vergrösserten Schilddrüse gemacht. Man fand in dieser kein Adenom, nur eine festere Partie in einer schwieligen Drüse. Diese Partie nebst um-

liegendem Gewebe wurde extirpiert. P. A. D. (Gellerstedt): »Man findet im Thyreoideagewebe, in den interlobären, chronisch entzündeten, infiltrierten Bindegewebesepten zahlreiche Epitheloidzelltuberkeln mit einzelnen Riesenzellen. An einer einzigen Stelle Andeutung zentraler Nekrose in einem Tuberkel. Nur unbedeutende Induration einiger Tuberkel. Keine Fremdkörper weder innerhalb noch ausserhalb der Riesenzellen. Ein einziges säurefestes Stäbchen in einem Hallberg-Präparat¹ aus dem Innern eines

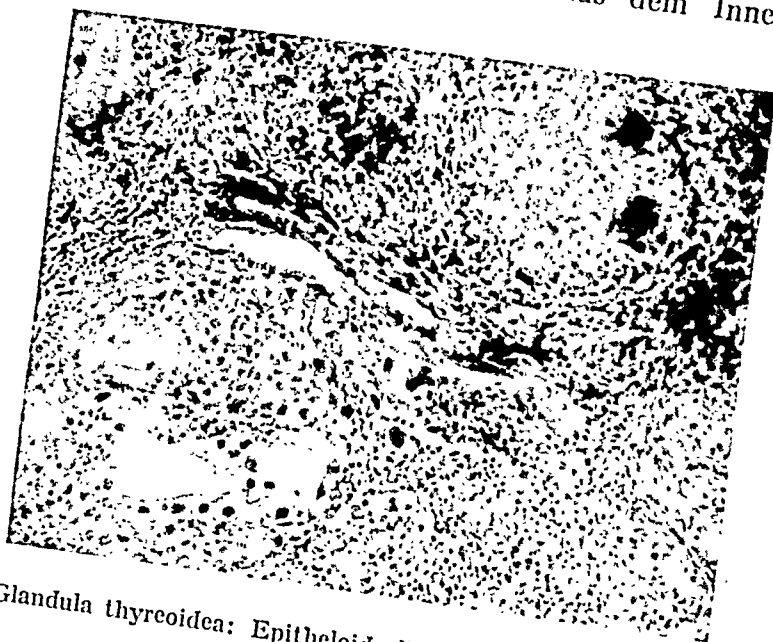


Fig. 2. Glandula thyroidea: Epitheloidzellstuberkeln mit Riesenzellen ohne deutliche Nekrose.

Tuberkels. Indessen zeigt die Thyreoideaprobe noch eine ganz andere Veränderung, nämlich eine intensive Basedow-Veränderung. Im Hinblick auf den Bazillenfund und die Tbc-ähnlichen Veränderungen in der früher untersuchten Tränendrüse dürfte kein Anlass vorliegen, tuberkuloide Herde zu vermuten, wie sie zuweilen in Basedow-Struma vorkommen. Statt dessen dürfte der Befund als eine Tbc-Affektion gedeutet werden können» (Fig. 2 u. 3).

¹ Färbung der Tuberkelbazillen nach Hallberg.

Das Ausstrichpräparat wird auf gewöhnliche Weise getrocknet und fixiert. Übertropfung mit Nachtblau (Grübler & Co) in einer Konzentration von $\frac{1}{4}$ — $\frac{1}{2}$ % in 2.5 % Karbolsäurelösung. Erhitzung bis zur Dampfbildung. Abfärbung in salzsaurem Alkohol (70 %). Nach Wasserspülung Kontrastfärbung mit Neutralrot, verdünntem Karbolfuchsin oder Vesuvin. Wasserspülung. Luft-trocknen. Die Tuberkelbazillen werden dunkelblau gefärbt.

Die Thyreoideauntersuchung öffnete also neue Aspekte. Es scheint zunächst angebracht, in Kürze das Problem der typischen Tbc in der Glandula thyroidea zu berühren. Um 1860 erklärte Rokitanski, dass die Schilddrüse nie von Tuberkulose angegriffen werde. Einige Jahre später beschrieb Virchow zwei Fälle von Miliar-Tbc mit Thyreoideaänderungen. Er betrachtete dies als eine grosse Seltenheit und war ebenfalls der Meinung, dass die Schilddrüse mehr als irgendein anderes Organ gegen Tbc-Infektion



Fig. 3. Glandula thyroidea: Verflüssigung des Kolloids, Epithelwucherung und Lymphocyteninfiltrate.

geschützt sei. Nach dem Urteil solcher Autoren war es kein Wunder, dass diese Ansicht in der Mitte des vorigen Jahrhunderts ganz und gar dominierte. Demgemäss sandte man Tbc-Patienten nach Strumagegenden, um ihnen möglicherweise den Kropf zu verschaffen, der ihre Krankheit günstig beeinflussen könnte. Die umfangreiche Literatur, die nach der genannten Zeit dieses Thema behandelt hat, lehnt in der Hauptsache das gegensätzliche Verhältnis zwischen Thyreoidea und Tuberkulose ab. An mehreren Stellen meint man sogar einen Beleg dafür zu haben, dass die gewöhnlichste unserer Thyreoideakrankheiten, die Hyperthyreose, durch Tuberkulose in der Schilddrüse verursacht sei (Costa, Holmgren, Mosiman, Uemura u. a.).

Als Komplikation zur Tuberkulose in den Lungen oder in einem

anderen Organ tritt diese Krankheit in der Thyreoidea hauptsächlich in zwei Formen auf. Am gewöhnlichsten ist ohne Zweifel eine diffuse Aussaat von Tuberkeln bei der akuten Miliartuberkulose, wobei die Veränderungen in der Thyreoidea sich kaum von denjenigen in anderen Organen unterscheiden. Die andere Form tritt bei avancierter Lungentuberkulose auf und erscheint zunächst als eine diffuse Sklerosierung der Drüse. Im letzteren Fall sind keine Tuberkelbazillen zu finden; der Prozess ist als Resultat einer allgemeinen Toxinwirkung aufzufassen. Bedeutend seltener sind die Fälle, bei denen der tuberkulöse Prozess sich in der Hauptsache zur Glandula thyreoidea zu begrenzen scheint. Im Jahre 1932 schilderten Rankin und Graham aus der Mayo-Klinik 20758 operierte und mikroskopisch untersuchte Strumafälle. Bei 21 dieser Fälle, also in einem Falle von tausend, lagen Tbc-Veränderungen vor, meistens in Form von diffus verstreuten Epitheloidzelltuberkeln mit Riesenzellen. Einzelne Fälle wiesen Konglomerattuberkeln und kalte Abszesse auf. Eine Angabe von Bazillenfunden wird in diesem Material nicht mitgeteilt. Die Absicht der Verfasser war vor allem, charakteristische klinische Symptome der Schilddrüsentuberkulose zu erforschen. Von diesem Gesichtspunkt aus wurde das Resultat negativ. Rankin und Graham fanden in der früheren Literatur 104 klinisch beobachtete Fälle von Schilddrüsentuberkulose, von denen nur 2 vor der Operation diagnostiziert waren (Borri, Nather). Harjola vermehrt die Anzahl der Fälle in der Literatur mit 28 und beschreibt selber 2. Er macht darauf aufmerksam, dass man aus Mangel an charakteristischen Symptomen diese Diagnose bei erhöhter S. R., bei Leukopenie und harter Konsistenz einer vergrößerten Schilddrüse verdächtigen kann. In Rankin-Graham's Material wurde gewöhnlich nur $\frac{1}{2}$ — $\frac{3}{4}$ der Schilddrüse reseziert, auf Grund der Gefahr eines sekundären Myxödems in dem durch Entzündung stark veränderten Gewebe. Trotzdem entstand in einem der Fälle ein postoperatives Myxödem. Insgesamt hat sich in 3 von 125 operierten Fällen Schilddrüsentuberkulose ein Myxödem ausgebildet, das ohne Schwierigkeit mittelst Thyreoideamedikation gebessert wurde. Von Rankin-Graham's Patienten starb einer der operierten an Lungenembolie unmittelbar nach der Heimkehr vom Krankenhaus; ein weiterer starb 3 Jahre später an Herzinsuffizienz. Die übrigen befanden sich noch nach 5—6 jähriger Beobachtung bei guter Gesundheit und

zeigten keine Spur von Tuberkulose oder Thyreoideadysfunktion. Die genannten Verfasser bezeichnen also die Prognose dieser Fälle als unbedingt gut. Unter Rankin-Graham's 21 Fällen von Schilddrüsentuberkulose wurde in 15 Hyperthyreose mit Grundumsatz über 19 % konstatiert. In 8 dieser Fälle fand der Pathologe später sowohl Basedow- als auch Tbc-Veränderungen im Thyreoideagewebe. Die Frage, welche dieser Veränderungen als die primäre zu betrachten sei, lassen diese Autoren offen.

Coller und Higgins haben einen sonderbaren Fall beschrieben, der in diesem Zusammenhang von grossem Interesse ist. Eine 52-jährige Frau wurde nach der Diagnose Morbus Basedow operiert, wobei Resektion des einen Schilddrüsenlappens vorgenommen wurde. P. A. D.: Morbus Basedow. Zuzufolge beständiger Hyperthyreosebeschwerden wurde nach 10 Monaten der übrig geblieben Lappen reseziert. P. A. D.: Lugolisierte Morbus Basedow mit aktiver Proliferation und diffus verstreuten Miliartuberkeln. In dem Zeitraum zwischen den beiden Operationen hatte sich also in diesem Struma eine Miliartuberkulose entwickelt. Klinisch konnten im Zustand des Patienten keine Veränderungen auf Grund des zustossenden Tbc-Prozesses wahrgenommen werden.

In der überwiegenden Mehrzahl publizierter Fälle von Tbc in der Glandula thyreoidea wurde die Diagnose nach dem typischen histologischen Bild gestellt, ohne dass Bazillen nachgewiesen werden konnten. Hedinger fand jedoch Bazillen in 9 von seinen 10 Fällen. Nather teilt mit, dass Tuberkeln in der Thyreoidea nur eine geringe Anzahl Bazillen aufweisen und schreibt dies deren evtl. gesteigertem Zerfall daselbst zu.

Bei unserem Patient mit M. S. liegt offenbar ein Tbc-Prozess in der Glandula thyreoidea vor. Ein zufälliges Zusammentreffen von zwei so seltenen Krankheiten dürfte ausgeschlossen sein. Die Gewebeveränderungen in Glandula thyreoidea können sicherlich als eine Manifestation von M. S. gedeutet werden. Allein durch diese Lokalisation hat unser Fall ein kasuistisches Interesse. Er scheint indessen auch von einem anderen Blickpunkt aus beachtenswert, nämlich in bezug auf die Ätiologie von M. S.

Das für M. S. charakteristische pathologisch-anatomische Bild unterscheidet sich von demjenigen der klassischen Tuberkulose hauptsächlich dadurch, dass die Nekrosenbildung in den Hintergrund tritt und die Rundzelleninfiltration um die Epitheloidzell-

herde unbedeutend ist. Mehrere Verfasser betonen das gleichzeitige Vorkommen von M. S. sowie Tbc-Veränderungen und vermuten einen Übergang zwischen beiden (Mylius-Schürmann, Schaumann, Hantschmann).

Betreffs der Ätiologie von M. S. sind drei verschiedene Alternative angeführt worden. Die meisten Forscher sehen in M. S. eine Form von Tuberkulose, eine andere Gruppe nimmt an, dass M. S. eine selbstständige Infektionskrankheit sei, von unbekanntem Virus verursacht, und nach einer dritten Ansicht schliesslich wird die Veränderung als eine spezielle Gewebereaktion aufgefasst (Retikuloendotheliose), von verschiedenen Agentien verursacht, darunter Tbc, Syphilis und Lepra. Da in der überwiegenden Mehrzahl der Fälle Stützpunkte für syphilitische oder lepröse Infektion fehlen, ist die Fragestellung praktisch genommen diese: ist M. S. tuberkulös oder nicht?

Entscheidende Bedeutung hierbei hat der Bazillenfund. Dieser ist selten bei M. S., kommt jedoch vor. Bereits Boeck konnte in der Nasenschleimhaut eines seiner Sarkoidpatienten Tuberkelbazillen mittelst Inokulation am Meerschweinchen feststellen. In frischen Rundzellenherden, die 10 Tage nach einer Rezidivaussaat auftraten, hat Kyrle zahlreiche säurefeste Stäbchen nachgewiesen. Bei Probeexcision 11 Tage später waren die Epitheloidzellen in den Vordergrund getreten; Bazillen fanden sich auch noch, aber spärlich. Nach weiteren 5 Tagen wurde typisches M. S.-Gewebe konstatiert, in dem keine Bazillen zu finden waren. Auch Ruete konstatierte zahlreiche Bazillen in frischen Herden. Viele Meerschweinchenproben mit Material von Haut und Knochenmark sind positiv ausgefallen. Kiss-Meyer erhielt indessen negative Meerschweinchenproben in sämtlichen sorgfältig untersuchten Fällen. Es ist jedoch hervorzuheben, dass die positiven Fälle grössere Bedeutung haben (vgl. Schaumann-Hallberg, 1941), dass sie durch ihre Anzahl Zufälligkeiten ausschliessen dürfen und schliesslich, dass Kyrle's Untersuchungen von frühen Fällen auf eine Möglichkeit hindeuten, dass die Anzahl der positiven Befunde zu steigern sei. Negative Kultur- oder Inokulationsversuche sprechen übrigens auch nicht mit Bestimmtheit gegen Tbc, da man beispielsweise nur in Ausnahmefällen positive Probe bei gewissen Tuberkuliden findet. Schaumann rechnet mit irgend einer Form von Tbc-Virus als ätiologischen Faktor. Er hat im M. S.-Gewebe einen Teil diphte-

roider und streptotrixähnlicher Bazillen angetroffen, die sich nach Hallberg's Nachtblau-Methode färben. Als Ausdruck für diese Form von Tbc-Virus betrachtet Schaumann ebenfalls die Korpuskeln, die nicht selten in den Riesenzellen zu sehen sind. Andere Verfasser betonen, dass die erwähnten korpuskulären Elemente degenerierte elastische Fasern seien (Berg-Bergstrand).

Hinsichtlich der sicheren Bazillenfunde scheinen aber schwer wiegende Gründe für die Tbc-Ätiologie zu sprechen.

Die Gegner der Tuberkulostheorie, vor allem Kiss-meyer, stützen ihre Ansicht grösstenteils auf die allgemeine Beobachtung, dass kutane Tuberkulinproben bei M. S. gewöhnlich negativ ausfallen. Von den Fällen, bei welchen vollständige Tuberkulinuntersuchung gemacht wurde (Mantoux bis zu 1 mg) scheint ca $\frac{1}{3}$ noch nach 30-jährigem Alter negativ zu sein (Björnstad-Bonnevie). Gemäss späteren Forschungen ist diese herabgesetzte Tuberkulinempfindlichkeit vielmehr eine Stütze für die Tbc-Theorie geworden. J. Jadassohn (1914) konstatierte, dass Patienten mit M. S. gegen Tuberkulin weniger empfindlich sind als gewöhnliche gesunde, tuberkulinpositive Personen. Genannter Verfasser gründete daraufhin seine Theorie von der »positiven Anergie«. Diese Theorie hat in den letzten Jahren einen beweiskräftigen Beleg durch Lemming's BCG-Vakzinierungsversuche erhalten. Dieser Forscher konnte zeigen, dass M. S.-Patienten bedeutend schlechter auf diese schwach virulenten, bovinen Tbc-Bazillen reagierten als gesunde tuberkulinnegative Personen. Es ist daher wahrscheinlich, dass man früher der Tuberkulinprobe allzu grosse Bedeutung betreffs des Ätiologieproblems von M. S. beigemessen hat. Die negative Probe spricht nicht gegen die Annahme einer tuberkulösen Ätiologie.

In der Diskussion Tbc oder nicht Tbc muss noch die klinische Korrelation von M. S. zur klassischen Tbc erwähnt werden. Die Kombination von M. S. mit banaler Tbc in Haut und Lungen ist geschildert worden (Boeck, Jadassohn, Schaumann u. a.). Man hat auch Übergänge von der einen Affektion in die andere wahrgenommen. So hat z. B. Goldschmidt die Umwandlung von »Boeck's Sarkoid« in Lupus vulgaris beobachtet, während Volk die Entwicklung in umgekehrter Richtung bekräftigen kann (histologische Verifikation).

Die von uns hier beobachtete Patientin weist eine Tränendrüsenveränderung auf, deren Art typisch für M. S. ist. In der Thyreoi-

dea, die ausserdem eine intensive Basedowveränderung aufwies, fand man einen Prozess vom gleichen Typus wie in den Tränendrüsen, jedoch mit einer Andeutung zu Nekrosenbildung und positivem Bazillenfund. Wir haben die von Hallberg angewiesene Färbungsmethode benutzt, welche zuvor nur in wenigen Fällen von M. S. angewandt wurde. Es ist wohl möglich, dass man mit dieser Methode mehrere Fälle von M. S. als wirkliche Tuberkulose entschleiern kann. Von grossem Interesse ist Schaumann-Hallberg's Nachweis von Tbc-Bazillen in Drüsenpräparaten aus dem Jahre 1915, einem von Schaumann's ersten Patienten gehörend. Bei der damaligen Untersuchung war Pat. tuberkulinnegativ, auch die Meerschweinchenprobe der Drüsen fiel negativ aus.

Wie die Mehrzahl der in der Literatur geschilderten Fälle von Thyreoidea-Tbc zeigt auch unser Patient Symptome von Hyperthyreose. Ob ein Kausalitätszusammenhang vorliegt, ist auch in diesem Falle unklar. Indessen hat Pat. deutliche Beschwerden durch ihre Thyreotoxikose, weshalb aktive Therapie wünschenswert wäre. Der konsultierte Chirurg rät von Strumaecktomie ab vor der Gefahr eines sekundären Myxödems. Mit Rücksicht auf die oben angeführten Fälle von Thyreoidea-Tbc scheint dieses Risiko doch gering zu sein. Eine Selbstheilung der Hyperthyreose auf Grund der weiteren Ausbreitung des M. S.-Prozesses erscheint äusserst problematisch. Die Patientin selbst lehnt eine Operation entschieden ab. Sie erhält Röntgenbehandlung in kleinen Dosen und Sedativa, worauf das subjektive Wohlbefinden unter diese Behandlung bedeutend zugenommen hat.

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Hodgkin's disease of the skeleton.

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When the osseous changes in Hodgkin's granuloma has once caught our attention, it appears to be fairly common. If roentgenograms are regularly taken of the skeletal parts of patients suffering from Hodgkin's disease, it will appear that the bone is often unmistakably affected. Askanazy and Valetta were the first to recognize this.

The estimates of the frequency with which skeletal affections occur, varies exceedingly. Dresser, who studied 149 cases which in the clinic had been diagnosed as lymphogranulomatosis, found skeletal affections in 10 per cent. He observed, however, an important increase of this percentage (up to 75 per cent) when he confined his attention to patients in the ultimate stages of the disease. Craver and Copeland investigated 172 patients and noted the affection in 15 per cent. Geschickter remarks that a careful histological examination will nearly always reveal abnormalities in the bones that may be ascribed to the lymphogranulomatosis. Kimpel and Belot arrived at the same conclusion: «L'atteinte osseuse, quoiqu'un peu fréquente, n'est pas du tout exceptionnelle. Il suffit d'en avoir signalé l'existence et de la rechercher pour en voir se multiplier les cas».

Rathóczy goes even further, and expresses the opinion that, apart from the glands, the bones are the parts that are most frequently affected. In the Netherlands osseous changes in lymphogranulomatosis are described by Voorhoeve and Teenstra.

All these investigators studied cases which in the clinic had been recognized as Hodgkin's disease, but not rarely patients are met with in whom the only indication of this disease is found in lesions of the bones (Herscher, Krumbhaar, Blount, Pechel, Montgomery, Livingstone a. o.) The diagnosis is here by no means easy, for the skeletal changes revealed by the roentgenograms vary exceedingly. A reliable conclusion can only be drawn by biopsy and its careful histological examination. Five cases of Hodgkin's disease of the skeleton observed by us may here be adduced in corroboration of this view. In two of the patients the disease was recognized by clinical observation; in the three others the clinical symptoms were not sufficiently clear to allow the diagnosis Hodgkin's granuloma. Here only osseous changes were found, which afterwards proved to be due to lymphogranulomatosis.

Discussion of the five cases.

I. A man, aged 36, was seriously losing in weight. Three years previous to his admission to the clinic for internal medicine, he had developed a tumor on each side of the neck. These tumors lay behind the musculus sternocleido-mastoideus and above the clavícula. A biopsy was made and as it was found to be a case of Hodgkin's disease, the tumors were treated radio-therapeutically. As the patient complained also of pain in the right gluteal region, this part too was irradiated, after which the complaints ceased. Itch was never felt. Afterwards attacks of pain manifested themselves in the left shoulder and the left elbow. An anemia also developed, which at the time of his admission had reached a value of 37 Sahli. In several places lymphomas the size of a pigeon's egg were found. There were râles at the bases of both lungs, gurgling sounds were heard and a pericardial friction rub too was easily audible. By percussion the margin of the liver was detected four fingers below the arc of the ribs; the blunt margin of this organ could be palpated. The spleen was markedly enlarged, and protruded three fingers beyond the arc of the ribs. Once the blood was found to be eosinophilous, but a lymphopenia was constantly present. In the urine, especially during fever periods, a positive diazo-reaction was found, and the urobilin test too was always positive.

The *roentgenological examination* of the skeleton revealed the presence of diffuse affections of the os ilium dextrum and of the sacrum, manifesting themselves both in osteo-clasis and in osteo-sclerosis (cf. Fig. 1). In the

os ilium sinistrum a rather sharply outlined cavity is seen. The aspect suggests either a tumor with diffuse metastases, to wit a carcinoma, or an inflammatory tumor (lipo-granuloma, lymphogranulomatosis). The processus coracoideus sinister too showed a conspicuous osteosclerosis.

On account of his investigation the neurologist had suggested that metastases to the vertebrae or an affection of the medulla might be present. No involvement of the vertebrae, however, was found, but the osseous changes might be insufficiently advanced to show themselves in the roent-



Fig. I.

Rather sharply outlined cavity in left os ilium.

genograms. An investigation of the spinal channel, with the aid of lipiodol, might perhaps have yielded valuable results for the diagnosis (Kuckuck).

The phosphatase concentration of the blood was 9 U. per cent. The lues tests were negative; the sedimentation rate of the blood in the first hour was 100 mm. There was no jaundice (the test of Hymans van den Bergh was negative). The gelactose test showed nothing uncommon.

Patient was treated radio-therapeutically. After the first period of the treatment, he was allowed to go home. The hemoglobin concentration was now 52 Sahli.

When patient returned to the hospital for the second period of the treatment, he felt much better. The hemoglobin concentration nevertheless had remained the same. The phosphatase concentration had increased to 20 U. per cent. The test of Hymans van den Bergh was negative, that of Takata-Ara positive.

When patient was admitted for the third time, the phosphatase concentration of the blood serum had increased to 52.8 U. per cent. The tests of Hymans van den Bergh and of Takata-Ara were now both negative. The hemoglobin concentration had decreased. The roentgenograms showed no marked changes.

After patient had felt perfectly well for some months, he began to suffer from violent attacks of pain in the extremities and in the abdomen. Once more he returned to the hospital; he now had a high temperature with jaundice. It was clear to us that he had reached the final stage of a deadly disease. He went home in a cachectic condition and died shortly afterwards.

Summary: On account of his complaints roentgenograms were made of a patient, whose disease was diagnosed clinically as lymphogranulomatosis; they revealed extensive changes of the bones. As mainly bone destruction and osteo-sclerosis were found, the roentgenograms suggested a carcinoma with diffuse metastases.

II. In January and February 1939 a man, aged 30, had been treated radio-therapeutically in a hospital, because the lymphglands in his neck, elbows, groin and breast were swollen. A biopsy from one of the swollen glands (Dr. Rochat) revealed that it was a case of Hodgkin's disease. The Gordon test too had been found positive. For three or four months the radio-therapeutical treatment had yielded good results.

Three weeks before his admission to the Academical Hospital, hands and feet as well as ankles and knees began to swell. The syndrome at first suggested tuberculosis: decrease in weight, nightly perspiration, reduced appetite and pain in the chest. There was no itch. Lymphgland packets were palpated in neck, armpits and groin, but they were not painful. Further, the mediastinum was, as both physical and roentgenological examination showed, enlarged. Hands and feet were swollen, and in both knees liquor was found. On his breast a network of veins was clearly marked. Spleen and liver were swollen. The urine gave a strong urobilin reaction, and the sediment moreover contained erythrocytes. The kidneys were roentgenologically examined with the aid of abrodil, but showed no abnormalities. In the blood a strong lymphopenia (8 per cent) and a light anemia (68 per cent) were found; sedimentation rate of the blood reached in the first hour a height of 61 mm in the second 118 mm. Some weeks later these figures were respectively 125 and 147 mm. The lues tests were negative. The temperature fluctuated during the whole time between 38° and 39° C.

The roentgenograms revealed in both hands the presence of shadows extending along the entire length of the second and third phalanges and of the metacarpi (Fig. 2). Their aspect was peculiarly nebulous, and not unlike, but nevertheless not fully conform to that found in an ordinary periostitis, for they extended into the metaphyses. The feet and femora showed similar affections. (Fig. 3 and 4). Between the corticalis and the

proliferation a narrow transparent zone stood out. The nature of the tissue could not be ascertained by the aid of the roentgenograms. In the structure of the bone itself no abnormalities were visible. The Ca excretion was determined with Snapper's method, and was found normal. The protein spectrum and the Ca and P values of the blood too were not markedly changed. The phosphatase concentration was 25 and 21 U. per cent.

A heavy irradiation was of no avail. Soon after his discharge from the hospital, the patient died at home.



Fig. II.

Anomalies in conformance with an ordinary periostitis.

Summary: On account of his complaints, roentgenograms were made of the skeleton of a patient suffering from malignant granuloma. Periostitic changes proved to be present.

III. A man, aged 62, had been complaining already for six months of unbearable pain in the left shoulder. In his own opinion it was due to a trauma. In stooping he also experienced some pain in the back, but for the rest he felt well. He was not losing weight and his appetite was undisturbed. Apart from a gonorrhea when he was 27, he had never been ill.

Examination revealed no abnormalities in his organs. The proximal part of the left arm was swollen and smarted when touched. The arm was not red and showed no clinical signs of inflammation. The clinical examination revealed no deviations in the vertebral column or in the legs. The mobility of the vertebral column was but slightly reduced. No neurological symptoms were present.



Fig. III.
Anomalies in conformance with an ordinary periostitis.

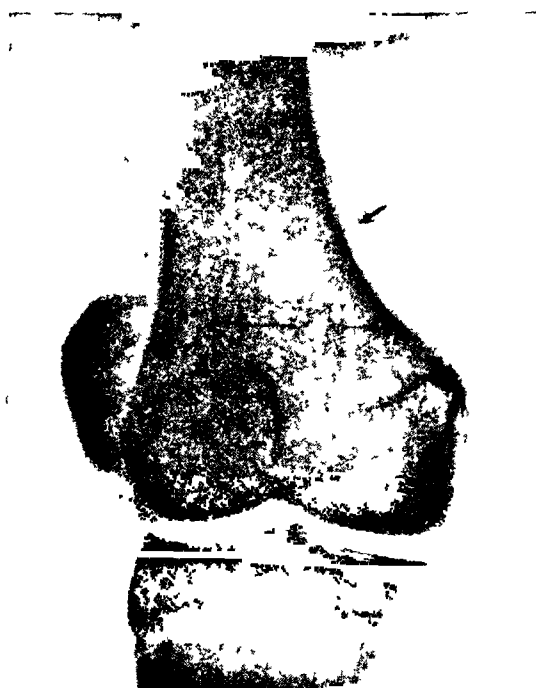


Fig. IV.
Anomalies in conformance with an ordinary periostitis.

The urine showed an alcalemic reaction; proteins, even that of Bence-Jones were absent; there was no reduction; the urobilin test was faintly positive; the diazo test negative every time.

The sedimentation rate of the blood was but slightly above the normal. A constant leucopenia of about 2500 and, moreover, a relative lymphocytosis were found. Degenerate cells were never seen. The cells of the bone marrow too showed a normal aspect. The proteins in the blood plasma were present in normal proportionality and in the usual amount. Ca and P



Fig. V.

Irregular tissue destruction, resembling a neoplasm.

concentrations of the blood serum too were normal. The alcalemic phosphatase, on the other hand, had strongly increased, and amounted now to 50 U. per cent. The various lues tests were, even after provocation with neosalvarsan, negative; and this applies also to the complement fixation gonorrhea test. The cholesterolin concentration of the blood serum remained normal and static.

Röntgenological examination.

Arm: the left humerus showed in its upper half marked changes, mainly consisting of transparent areas indicating parts where the bone had disappeared. Between these areas parts of the bone tissue were still visible. The left scapula showed mainly osteo-sclerosis. Neither in the humerus

nor in the scapula a well-defined periostitis was to be seen. The changes in the humerus indicated an irregular tissue destruction of the kind found when the bone is affected by a neoplasm or an inflammatory tumor (Fig. 5).

Pelvis: here mainly extensive osteo-sclerosis and but little tissue destruction was found; the affected parts showed a woolly aspect in the roentgenogram. The os pubis dextrum was strongly thickened, and showed irregular and hazy outlines. Here the formation of new bone prevailed. The aspect suggested Paget's disease (Fig. 6).

Not only the roentgenogram of the pelvis, but the constantly supra-normal phosphatase concentration of the blood serum too, seemed to point in



Fig. VI.

Alterations suggesting Paget's disease.

the direction of Paget's disease (ostitis deformans). The aspect of the caput of the left humerus in the roentgenogram, on the other hand, suggested a malignant tumor. The phosphatase increase of the blood serum is not to be regarded as a fully reliable indication of Paget's disease, for when the bone tissue is affected by carcinoma metastases, a similar increase may be found. The roentgenologist, however, was so much impressed by the pathological changes of the pelvis that he considered Paget's disease more likely; according to Schmorl changes in the pelvis should occur in 22 per cent of the patients suffering from this disease, whereas affections of the humerus found in 4 per cent only. As the Ca and P values of the blood as well as the excretion of calcium which, on application of the diet prescribed by Snapper, was found in the urine, proved to be normal, Recklinghausen's disease was improbable. Against Kahler's disease pleaded the absence of

Bence-Jones protein, the affection revealed by the roentgenograms, the normal protein concentration in the blood plasma, the absence of degenerate cells in the sternal punctate, and the well nourished condition of the patient. No more could it be an storage-disease.

Although biopsy made from the caput of the left humerus did not confirm the diagnosis: Paget's disease (the result of the assay was: non-specific inflammation accompanied by cell proliferation), the usual therapy for this disease (A. T. 10 and vitamines A en D) was applied. The pain,

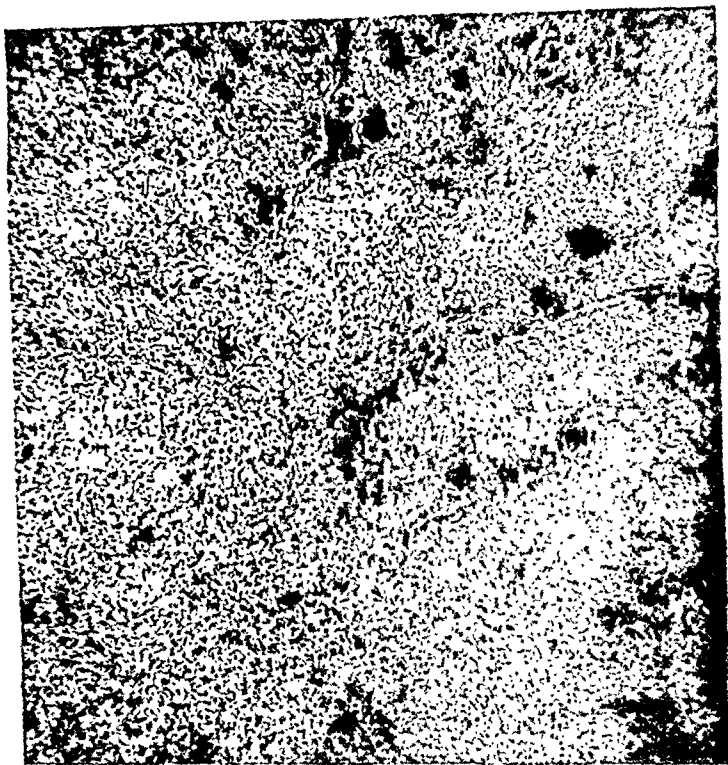


Fig. VII.

Necrosis and cellular inflammation with proliferation of the connective tissue (malignant granuloma) magn. 50 \times .

however, persisted and intensive irradiation of the whole skeleton, and especially of the left scapula, did not alleviate the pain, nor did it stop the process. Then a spontaneous fracture of the upper arm manifested itself, and as all attempts at a conservative therapy failed, an exarticulation of the arm was decided on, but this measure too had but a temporary success.

The histological examination of the arm indicated malignant granuloma (cf. Fig. 7). Fig. 8 shows no attacking of the cartilage of the upper arm by the malignant granuloma. To see whether the disease was confined to the skeletal parts, an inguinal lymph gland was extirpated, but this was found unaffected. As the roentgenogram suggested a decalcification of the left humerus, this bone was chemically analysed (cf. table). Indeed, an



Fig. VIII.

Cut surface of humerus of pat. III, showing undamaged cartilage.

increase of the organic constituents and a decrease of the anorganic ones were found. Similar values occur in osteitis fibrosa, tumors of bone and other diseases affecting the bony tissue.

This patient too passed away after a period of violent suffering.

Chemical constitution of part of the humerus of patient III.

	ash	organ. const.	P	Ca
humerus of Pat. III	44 80	55 20	7.86	19.20
normal humerus	61 46	38 24	10.56	26.54

Summary: Roentgenograms of a patient with an affection of the left upper arm and of the pelvis revealed changes in the skeletal parts, those of the pelvis suggesting Paget's disease, those of the left upper arm a malignant tumor or an inflammation tumor. The histological assay afterwards showed that the changes in the bones were due to Hodgkin's disease, which apparently was confined to the skeletal parts.



Fig. IX.

Mixed osteolytic and sclerosing alterations.

IV. A woman, aged 27, had already for 2 ½ years experienced pain in both knees when walking. Apart from a slight atrophie of the calf of the right leg no anomalies were found. The clinical examination revealed no organic defects.

The roentgenograms showed in the upper part of the right tibia a diffuse involvement extending upwards to the condyle (Fig. IX and X). It consisted mainly of osteo-sclerosis accompanied by osteo-clasis. On the lateral face the corticalis was thinned. At the lower end of the femur too changes of this kind, though less conspicuous, were found. The strongly pronounced destruction of tissue suggested the diagnosis sarcoma, but the extension to the femur made this somewhat doubtful.

A biopsy of the affected bone revealed a proliferation of cells accompanied by necrosis.

Patient had to leave the clinic, but returned six months later. Her general condition had deteriorated. The inguinal lymph glands were found enlarged. Roentgenograms revealed an extension of the affection of the right tibia and femur. The focus in the right tibia was once more excochleated; this time the histological examination led to the diagnosis: Hodgkin's granuloma (fig. XI). Biopsy of a lymphoma from the right side of the



Fig. X.

Mixed osteolytic and sclerosing alterations.

groin showed conspicuous centres of proliferation, but no indication of Hodgkin's disease. The other parts of the skeleton showed no affection. The urine was normal; Wassermann's test negative. Apart from a lymphocytosis amounting to 48 per cent, the blood too was normal. The sternal punctate contained no abnormal cells. The Ca and P as well as the cholesterol concentration of the blood serum were normal. The phosphatase concentration of the blood was 10 U. per cent. The excretion of calcium through the kidneys, determined by the aid of Snapper's method, showed no increase.

Patient was treated with roentgen rays. A considerable time after she had left the clinic, her decease was communicated to us.

Summary: On account of the roentgenological examination the disease of a female patient with an affection of the right tibia and femur, was preliminarily diagnosed as sarcoma. The biopsy, however, revealed that the affection of the bone was due to Hodgkin's granuloma. Apart from the lesions found in the right leg, no defects were observed in the skeleton. The phosphatase concentration of the blood was 10 U. per cent. Clinical indications of Hodgkin's granuloma were absent.

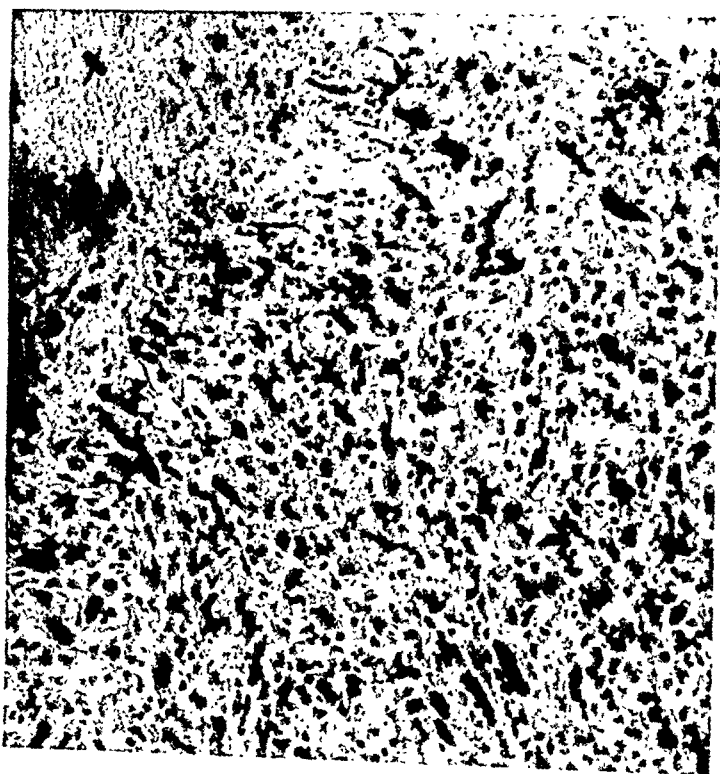


Fig. XI.

Focus in the tibia. Necrosis (X) and polymorphic connective tissue, with giant cells.

V. A little girl, aged 5, had been complaining already for five or six weeks of pain in the left shoulder, especially when she changed its position. Apart from a painful, slightly fluctuating swelling on the left scapula, no other abnormalities were found. Aspiration of the swelling only produced a small quantity of blood. Swollen lymph glands were not observed.

Roentgenograms of the left scapula showed the presence of some irregularly outlined transparent area (Fig. XII). Especially in the centre the destruction of tissue was considerable. The lesion might have been due to a sarcoma, but a similar aspect may also be caused by an inflammation. Other parts of the skeleton showed no defects.

Excochleation of the focus was decided on. It proved to contain a cavity filled with a vitreous tissue. It seemed to be a case either of sarcoma or of osteomyelitis. In the bacteriological investigation some colonies of staphylococci were obtained from the tissue, but the presence of these organisms may be due to a secondary contamination.

The histological assay of the tissue revealed the presence of granulation tissue, eosinophilous leucocytes and giant cells of Sternberg, and the affection was therefore recognized as a case of malignant granuloma. The blood



Fig. XII.

Irrregular tissue destruction of the scapula.

showed 51 per cent lymphocytosis and 7 per cent eosinophilia. In other respects it was normal: the phosphatase concentration was 3 U. per cent; Wassermann's test was negative; the Ca and P concentrations in the blood serum were quite normal; the various constituents of the protein spectrum of the blood plasma were present in the normal proportion.

A heavy irradiation of the affected bone was decided on. On account of this treatment the complaints disappeared almost completely, and roentgenograms taken at a quarterly control in the out-patient's department showed an improvement of the affection in the left scapula. New foci were not seen. The only disquieting symptom was the increase of the phosphatase concentration of the blood serum to 25 U. per cent.

Summary: Roentgenograms taken of a little girl patient with an affection of the left shoulder, revealed the presence of irregularly outlined transparent area in the left scapula, which suggested a sarcoma. The histological assay proved that the lesion of the bone was due to Hodgkin's granuloma. Involvement of other parts of the skeleton could not be detected. Clinically no indications for the diagnosis Hodgkin's disease were present.

The exposition given above, leads to the two following conclusions:

1° malignant granuloma may be confined to skeletal parts (cf. cases III, IV and V);

2° roentgenograms of skeletal parts affected by Hodgkin's granuloma show an exceedingly variable character, and this disease, therefore, can not be diagnosed in this way. In the cases described above the osseous changes were ascribed three times to sarcoma, once to carcinomatosis, once to Paget's disease, and once to periostitis!

Other authors too have pointed out that in cases of Hodgkin's granuloma the aspect of the roentgenograms is exceedingly variable.

Roentgenologically two main forms can be distinguished, one in which bone destruction and decalcification of the skeletal parts prevail, and one in which the formation of new bone and osteosclerosis are of more importance. The sclerosis may be so strong that Hultén in a case of Hodgkin's granuloma of the vertebral column spoke of an »Elfenbeinwirbel» (ivory vertebra). A peculiar aspect is obtained when formation of new bone and bone destruction go side by side (cf. patients I, II and IV). In the vertebral column the bone destruction may be localized in the processus transversi and spinosi, whereas in the corpus osteosclerosis is found. These processus are apparently often affected by this disease, and this applies also to the osteophytes caused by an accidentally present arthrosis deformans. The intervertebral discs remain as a rule intact. Reisner and Brada however, found an affection of the latter in two cases, and Tetzner in one. Noteworthy is the affection of the periost: when present, it appears, as a rule, in the form of periostitis ossificans (cf. case II).

It should also be pointed out that an affection of skeletal parts may be present although the roentgenograms reveal no sign of it.

This may happen so long as the affection is confined to the bone marrow, and the trabeculae of the spongiosa remain uninjured.

As stated above, the roentgenological examination may be misleading: in the first place, because a negative result does not exclude the possibility that the bone nevertheless may be affected, and secondly, because the lesions of the skeletal parts caused by malignant granuloma may be very similar to those caused by other diseases (cf. the cases described above).

When the affection is confined to the skeleton, and the clinical aspect of the disease, therefore, does not resemble that of Hodgkin's disease (no lymph gland packets, no dilatation of the mediastinum, and no swelling of the spleen), the question can only be decided by biopsy. Cases IV and V are good examples of this: the preliminary diagnosis »sarcoma» was shown to be wrong, for the focus in the tibia and the scapula appeared to be a lymphogranulomatosis.

When are we allowed to conclude that a bone is affected? In those cases in which the patient merely feels a pain in the bones, but where physical and roentgenological examination fail to reveal defects, the diagnosis sometimes requires a protected period of observation. In these cases the pain sometimes precedes the roentgenological manifestation of the affection by years. Where multiple involvements of the skeleton are present, the increase of the phosphatase concentration may perhaps be useful. In this respect case V deserves our attention. The transparent area in the left scapula, histologically diagnosed as malignant granuloma, was here so far the only symptom of the disease, for nowhere else in the skeleton affections showed themselves in the roentgenograms. Nevertheless a diffuse, roentgenologically not yet visible affection of the skeleton might, on account of the increase of the phosphatase concentration of the blood, be present. The further clinical development will show whether this supposition is right or wrong. There are various possibilities. It is known that some diffuse affections of the skeleton (Paget's disease, Recklinghausen's disease, rachitis, bone carcinosis, a. o.) may cause an increase of the phosphatase concentration of the blood serum. These diseases belong to those in which a supranormal osteoclastic activity stimulates the development of new bone. The proliferating osteoblasts probably contain a large amount of phosphatase, part of which is given off to the blood (C. L. de Jongh). Then it should also be borne in mind that Hodg-

kin's granuloma is often accompanied by an affection of the liver: Terplan a. s. found on obduction in 50 per cent of his cases lympho-granulomatous foci in this organ, and it is known that in liver diseases also the phosphatase concentration of the blood is enhanced. Therefore, an increase of the phosphatase concentration of the blood should not be considered conclusive evidence of a skeletal affection. Here more facts will have to be collected!

What bones are most often affected? Actual observation shows that Hodgkin's granuloma shows a predilection for those bones that are rich in hematopoëtic tissue, i. e. mainly the flat bones (vertebrae, pelvis, ribs, sternum and, rarely, scapulae). In children other parts of the skeleton may also be affected. If the long bones are attacked, the proximal part is the first to suffer (cf. cases III and IV), the lesion occasionally causing a spontaneous fracture (case III). In the vertebral column the upper lumbar and lower thoracic vertebrae are most often attacked, rarely the cervical ones. Uehlinger, who studied 83 cases, came to the following arrangement:

Vertebrae	52 = 62.6 per cent	ribs	9 = 10.8 per cent
Pelvis	18 = 21.8 per cent	scapulae	2 = 2.4 per cent
Sternum	13 = 15.7 per cent	claviculae	2 = 2.4 per cent

The vertebral column may collapse, but without forming a conspicuous gibbus, such as is caused by tuberculous affection. The intervertebral discs, and herein too the affection distinguishes itself from spondylitis tuberculosa, remain as a rule intact. The cartilage is rarely attacked by the malignant granuloma (cf. Fig. 8).

One of the most important and earliest symptoms of an affection of the skeleton by Hodgkin's granuloma is the spontaneous, sometimes lancinating, but usually dull and gnawing pain sensation. All our patients complained of pain in the affected bones.

The cause of the violent pains experienced by patients suffering from lymphogranulomatosis maligna of the skeleton, is unknown. If the vertebral column is affected, it might be surmised that the pain is due to the collapse of this organ, but it has been found that in such cases a treatment with roentgen rays may alleviate the pain without altering the curvature. Patient III suffered unbearable pains in the left arm, but amputation of the arm did not remove the pain. Repeated injections of novocain in the stellate ganglion

and the latter's extirpation yielded not even a temporary success, and a heavy irradiation too was of no avail. Large doses of morphia were the only expedient mitigation, but the relief, of course, was but temporary.

The cause of the pain experienced by patients suffering from Hodgkin's granuloma may be found in the pressure exercised by the lymphomas on the nerves, but the nerves and their roots may also be taken ill by the infiltration of the lymphogranulomatous tissue, and this too may cause unbearable pain (changes in the dura have been described which, according to some authors, might be responsible for the pains). Ravie regards the lympho-granulomatous perivascularitis and obliteration of the vessels also as causes of the pain.

The differential diagnosis should discriminate between malignant granuloma and:

1° tuberculosis. In Hodgkin's granuloma of the vertebral column abscesses are usually absent; Fränkel, Much and Düring, however, described paravertebral ulcers. In contradistinction to tuberculosis the cartilage remains intact; in tuberculosis, moreover, the adjoining bone is, as a rule, atrophied. It does not give rise to gibbus.

2° multiple myeloma. In this affection the protein spectrum is changed, and the urine contains protein of Bence-Jones.

3° primary bone tumors.

4° carcinoma and hypernephroma metastases to the bones.

5° leukemia,

6° Paget's disease.

7° osteitis fibrosa generalisata.

8° bone cysts.

9° osteochondritis dissecans.

10° chronic osteomyelitis.

Therapy:

Various authors, e. g. Louste, Thibaut a. o. have warmly recommended the application of irradiation. Especially high penetrating X-rays should be used. As the affection of the bone, independent of any therapy, may lessen or remain stationary for several months, the interpretation of the results obtained with this treatment should be very cautious. Dresser is of opinion that the bones

should be treated with more r-units than the lymph glands. Irradiation of the lymphomas alone is of no avail. On the whole opinions with regard to the effectiveness of the radio-therapy diverge widely. Some authors (Reisner and Brada) believe that the irradiation causes the bones to regain their strength by Ca absorption; others suggest that the treatment merely alleviates the pain. Joly thinks that in cases of Hodgkin's granuloma accompanied by extensive bone destruction, the latter does not readily recalcify.

The affected bones only should be exposed to the rays. An exposition of the whole body should be avoided, as this may cause serious anemias which, even by the aid of repeated blood transfusions, are difficult to overcome.

The treatment should be started as early as possible, i. e. when there is a mere suspicion of malignant granuloma, and it should not be postponed until the roentgenograms begin to show the affection. Apart from the irradiation immobilisation is of great importance. Remissions are always possible with affections of this kind.

The first patient said he felt better after the irradiation, but the improvement was never objectively confirmed. The second patient succumbed at home, notwithstanding a strong irradiation. In the third patient, who died at home 1 ½ year after his first admission to the hospital, the condition of the affected bones did not improve, nor was the pain alleviated. No more did the fourth patient react on a heavy irradiation; a half year after her admission to the Department of Surgery, she died at home. The fifth patient has been under treatment for a short time only so that we are as yet unable to draw a conclusion. We are unable to give a definite opinion on the efficiency of the irradiation, but up to now our results are not promising.

Summary.

Five patients of different age and sex, suffering from malignant granuloma of the skeleton are described. It appears that this affection may be confined to skeletal parts (3 cases). The roentgenograms showed diverging aspects (sarcoma, carcinomatosis, periostitis, Paget's disease) so that a diagnosis could not be based on them. Histological assay proved imperative.

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REVUE DES LIVRES:

Fanconi & Wissler: Der Rheumatismus im Kindesalter. Teil 1:
Der Rheumatismus verus und seine Differentialdiagnose. 180
Seiten, 28 Bilder. Preis geb. RM 10: —. Verlag Theodor Steinkopff
Dresden und Leipzig 1943.

In der vom Verlage herausgegebenen Sammlung von Monographien, die den »Rheumatismus« behandeln, haben der berühmte Züricher Kinderarzt Professor Fanconi und sein klinischer Kollege den paediatrischen Teil des Stoffes übernommen. Im vorliegenden Band I wird ein gesonderter Teil abgehandelt, *Rheumatismus verus*, worunter die Verfasser die Krankheit verstehen, die mit Gliederschmerzen, Herzsymptomen oder Chorea einhergeht. In einem späteren Teil folgen die chronischen Polyarthritiden. Die Verfasser führen ihre Aufgabe mit grossem Eifer durch. Der umfangreiche Stoff lässt natürlich Raum für Vorbehalte und Erörterungen und kann bei dem augenblicklichen Stand unserer Kenntnisse nicht exakt behandelt werden. Als Ausdruck dafür darf man es wohl ansehen, dass das Kapitel Symptomatologie und Differentialdiagnostik ungefähr 2/3 der Seitenzahl des Buches beansprucht. Das Buch hat seinen Wert darin, dass es die persönlichen Beobachtungen eines erfahrenen Klinikers wiedergibt, wobei Apparatdiagnostik, Statistik u. s. w. ihren begrenzten Umfang erhalten, was nach Ansicht des Referenten wohlthuend empfunden wird. Die recht zahlreichen Krankengeschichten liefern vielleicht den grössten Ertrag.

Das Buch dürfte eine gewisse Lücke ausfüllen und die Verfasser haben mit massvoller Anspruchslosigkeit Klarheit in unseren Wissenstoff zu bringen gesucht.

B. Söderling, Borås.

Ouvrages envoyés aux *Acta medica Scandinavica*.

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From the St. Josephs Hospital in Porsgrunn, Norway. Physician in chief:
A. Schrumpf.

A case of hyperparathyroidism.

By

A. SCHRUMPF.

(Submitted for publication October 15, 1942.)

In the later years, an increasing number of cases of hyperparathyroidism (later on abbreviated to hp.) have been published. In 1940 about 200 cases of this interesting and important disease had been operated on, since Mandl (1) fifteen years earlier operated on the first known case.

In the Scandinavian countries as well this disease has been observed and described. In Sweden Ask-Upmark (2) has published 4 cases since 1931, Hellström (3) since 1932 4 cases, Wijnbladh (4) 2 cases. Single observations are published by Møller (5) (1936), Andersson (6) (1938), Østling (7) (1939), Kohler (8) (1940) and Jelke (9) (1940). In Denmark Schaldemose (10), Chievitz & Olsen (11), Schwensen & Eiken (12), Sørensen (13), Strandgaard (14), Friederichsen (15), Schultzer (16), Holten (17), Frank & Hjerrild (18), Schmith (19), Mortensen (20) (two cases), Nielsen & Steffensen (21) (two cases), have contributed to our knowledge. From Finland no case seems to have been published until now. In Norway the first case observed and successfully operated on, was published by Schrumpf & Harbitz (22) in 1938. Later on new cases have been described from Norway by Malm (23) (1939), Gulowsen (24) (1939), Hegge (25) (1939), K. Nicolaysen (26) (1941), J. Holst (27) (3 cases) and Eitinger (28) (1942). The last case was diagnosed in the Rønvik asylum and is comprised in the 3 cases operated on by

J. Holst. Until now, as far I know, 14 cases have been published from Denmark, 15 cases from Sweden and 8 cases from Norway. In 1942 I got the chance to diagnose a new case of hp. with typical skeletal findings, so that the total number of cases observed in Scandinavia amounts to about 38. This number is sure to rise in future, with the increasing knowledge of this disease among physicians. It is of great importance that the diagnosis should be made as early as possible to improve the results of surgical treatment of the disorder. As the disease develops further, irreparable renal changes, which no successful operation can alter, may be the result. The following case is presented as a contribution to widen our knowledge of hp. and to discuss some observations in connection with this case.

A 60 year old farmer O. Ø. was sent to me by a practitioner, who asked my opinion about the possibility of using gold treatment in the case presented. The examination in connection with X-ray of the right hip joint gave me the opportunity to diagnose hp., whereupon the patient was hospitalized for closer investigation. His journal runs as follows: Both parents died old. His father acquired diabetes as old. His wife, 2 children and 1 sister are healthy. His wife was operated on for struma several years ago. The patient himself was never sick until 3 years ago. At this time he observed slight pains in the right hip, but paid no special attention to them. One day he got so severe pains at the same spot that he could not stand upright. He was forced to lie in bed, whereupon the pains vanished. After keeping his bed for some days he was able to walk with a stick. Since then pains of the same localization have troubled him continually, especially when mounting stairs and going up hills. On flat roads he was able to walk 2—3 kilometers without pain. He has been practically disabled for work on his farm. Since the autumn 1941 his trouble increased. He got pains in his right shoulder and could not use his arm as usual. The pain disappeared as long as he kept quiet. Shortly after his right knee was affected, with pains irradiating from the hip region downwards into thigh and leg. Primo December 1941 the right elbow was affected, with distinct pain localized to the medial condyl of the humerus, with pains irradiating into the right hand and fingers. There was marked weakness of the right hand, while the sensibility in the hand was intact. Some days later he observed a tumefaction of the back of the right hand, close to the proximal part of the 3. metacarpal bone. This tumefaction still persists. From this time he stayed in bed, but without any important improvement of his condition. Stiffness as well as pain gave him almost continuous trouble. During rare intervals he was able to leave his bed. On one single occasion he got nausea and vomited. His voice is hoarse, but was normal before. A dry cough has been present for some time, swallowing is not disturbed. Neither back pain

nor renal colic ever troubled him. Appetite was good until lately, when he began to lose weight. Micturation has been frequent, with intervals from 2—3 hours. Diuresis was high as well during day and night time. Stool passage was normal at daily intervals. During bedrest he was somewhat constipated.

Status on the 7th of Januari 1942: The patient is a man neither fat nor undernourished, his appearance corresponding to his age. His skin is a little pale. No edemata are present. His mental activities are not troubled.



Fig. 1.

Temp. 37 C. Pulse 76, regular. Respiration not hindered. Blood pressure (Riva-Rocci) 160/90 mm. Extensive dental caries in the upper jaw, in the lower jaw the teeth are long with a thick layer of tartar. Pupillar reaction is normal as well for light as for accomodation.

Collum: In the jugular region a tumor presents itself reaching from the fossa jugularis upwards to the left, where it disappears under the border of the sterno-cleidal muscle. The length is about 3 cm. The lower border disappears behind the collar bone, but during the glutation act the tumor moves upwards and presents itself about the size of a plum, sharply contoured and of elastic consistency. The lower border can be reached by one finger when swallowing (cf. photograph). No vascular murmurs can be heard over the tumour which seems not to have any relation to the thyroid gland. No glandular enlargements on the neck, no thyreotoxic eye symptoms. The skin is dry and warm.

Heart: Absolute dullness from the 4. rib and the left sternal border. Ictus in the 5. interspace in the medioclavicular line. Normal heart sounds.

Lungs: Sonorous percussion, vesicular respiration.

Abdomen: Some subcutaneous fat. Tympanitic percussion everywhere, no tumours nor resistance. No pain in the renal regions.

Liver: Dullness from the 6. rib to the costal border. Liver not palpable.

<i>Reflex examination:</i>	right	left
patellar	++	++
achilles	++	++
abdominal	+	+
plantar	V	V

Status localis: The right arm shows muscular atrophy. There is a distinct tremor, especially in the fingers. On the left arm there is only a slight tremor. Maximal flexion in the right elbow and radiocarpal joint causes pain. The patient complains of distinct pain along the volar side of the medial humerus condyl. The force of the right hand and fingers is markedly reduced, and movement causes pain. At the proximal part of the 3. metacarpal bone a compact tumour, 2—3 cm long is found close up to the 3. metacarpal bone.

Right lower extremity: Shows marked muscular atrophy. Tenderness is elicited by pressure or percussion in the trochanteric region, no tenderness elsewhere. Rotation, ab- and adduction is somewhat limited in the hip joint because of pain. Flexion is performed to a normal degree. Flexion of the knee joint is intact, extension causes some pain.

Lasègues phenomenon negative on both sides.

<i>Measurements of atrophy:</i>	right	left
thigh	42	44 cm
leg	29	30
arm	28	28½
forearm	12	13

Exploration: The right lobe of prostata is slightly enlarged, but of normal consistency and with movable mucosa.

Urine: sp. gravity 1012. Diuresis from 2.2—2.8 l. Acid reaction to litmus. Albumin: traces. Sugar and benzidin reactions negative. No pus. Microscopically isolated lymphocytes are found.

Blood examination: 6th of January 1942: Hb 80 % (Haldanes standard) (5½: 67 %); red bl. corp. 4.08 millions pr mm³, colour index 0.98. white bl. c. 13750. Differential count: metamyelocytes 3½ %, segmented cells 58.5 %, eosinophiles 4 %, basophiles 3½ %, lymphocytes 26 %, monocytes ½ %. Sedimentation rate 18 mm. (5½ = 45 mm). Meinerke reaction in blood = negative.

Urea clearance 9/1 42: Blood urea 75 mg %, (30/1: 52.5 mg %), max. clearance: 14. Standard metabolism 10/1: 103 %. Electrocardiogram

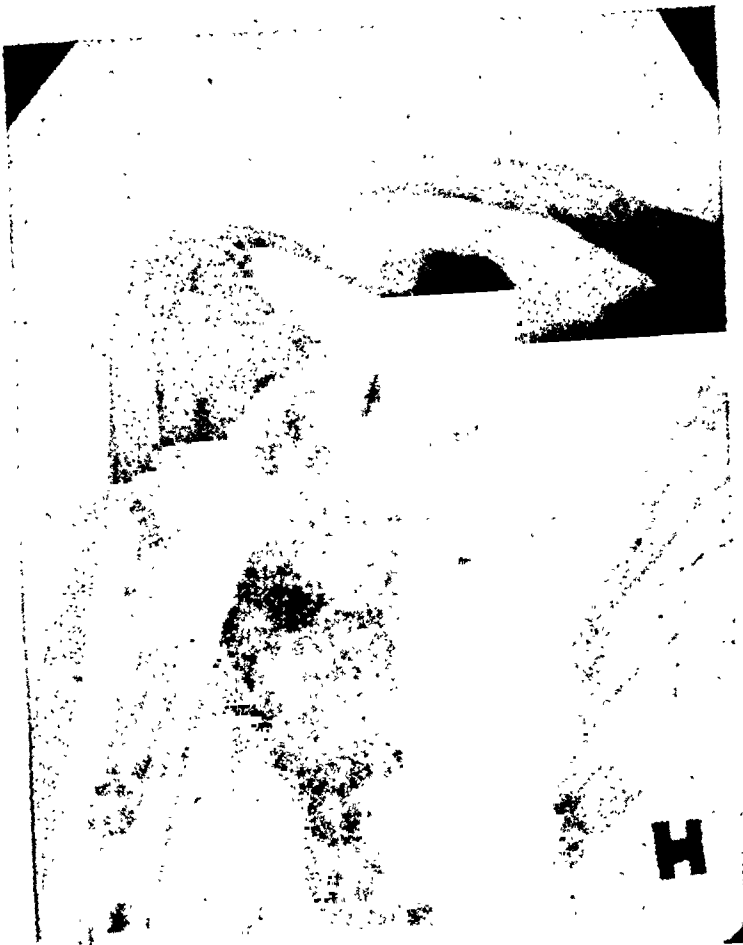


Fig. 2. Note the multiple medullary and subperiosteal cysts in the humerus and scapula.

8/1 42: Sinusrythm, frequency 60, left axis deviation, PQ 0.24, QRS 0.07, QT 0.34 sec. T positive in all leads.

X-ray examination: Heart size 15 $\frac{1}{2}$ cm, inner thoracic diameter 28 cm (distance 1.5 m). Trachea is dislocated to the right in the jugulum, the 7. right rib has spoolform in the axillar region. No calcium deposits in the lungs.

Right hip: Slight periartritic deposits in the hip joint. In the trochanteric region one area about 2 \times 3 cm and 2 smaller areas of lesser density are observed. A small, simular area is found in the os ischii. Similar areas of varying size are present in the scapula and humerus, in the mid-hand, ulna and probably in the right tibia as well (see photographs fig. 2—5.) No areas of lesser density are observed in the cranium.

The renal regions: The renal shadows are remarkably well visualized on both sides. Their size and position seem to be normal. No concrements are seen. The quantities of calcium, phosphorus, total base and carbon



Fig. 3. Note the multiple medullary and subperiosteal cysts in the ulna.

dioxide in serum are tabulated (see tab. I). The output of total base in the urines was registered pre- and postoperatively (tab. nr. 2). The patient never had fever during his stay. He was fed on an ordinary diet with 1 liter milk daily. In addition he received 1 spoonful codliver oil daily and 5 treatments by ultraviolet rays before the operation. His first weight was 69 kg, and 70.1 kg the 19th of January.

Diagnosis: The morbid history, the localization of a tumour up to the thyreoid region, the results of the X-ray examination in connection with an abnormally rised serum calcium and calcium excretion in the urines is highly suggestive for the diagnosis of hp. This diagnosis is fundamentally based on the rubbed calcium meta-



Fig. 4. Note the multiple cysts in the trochanteric region and the os pubis and os ischii.

bolism, marked by changes of the calcium value in the serum between 5.7—8.2 m. equ., as compared with the normal value of 5 m. equ. In the urines from 112 to 380 m. equ. of calcium was found. This last amount is without doubt pathologic and representative of what can be found in cases of hp. only.

The patient was delivered to the surgical unit (Porsgrunn Lutherske Sykehus), and operated on the 21th of January by dr. G. Ræder.

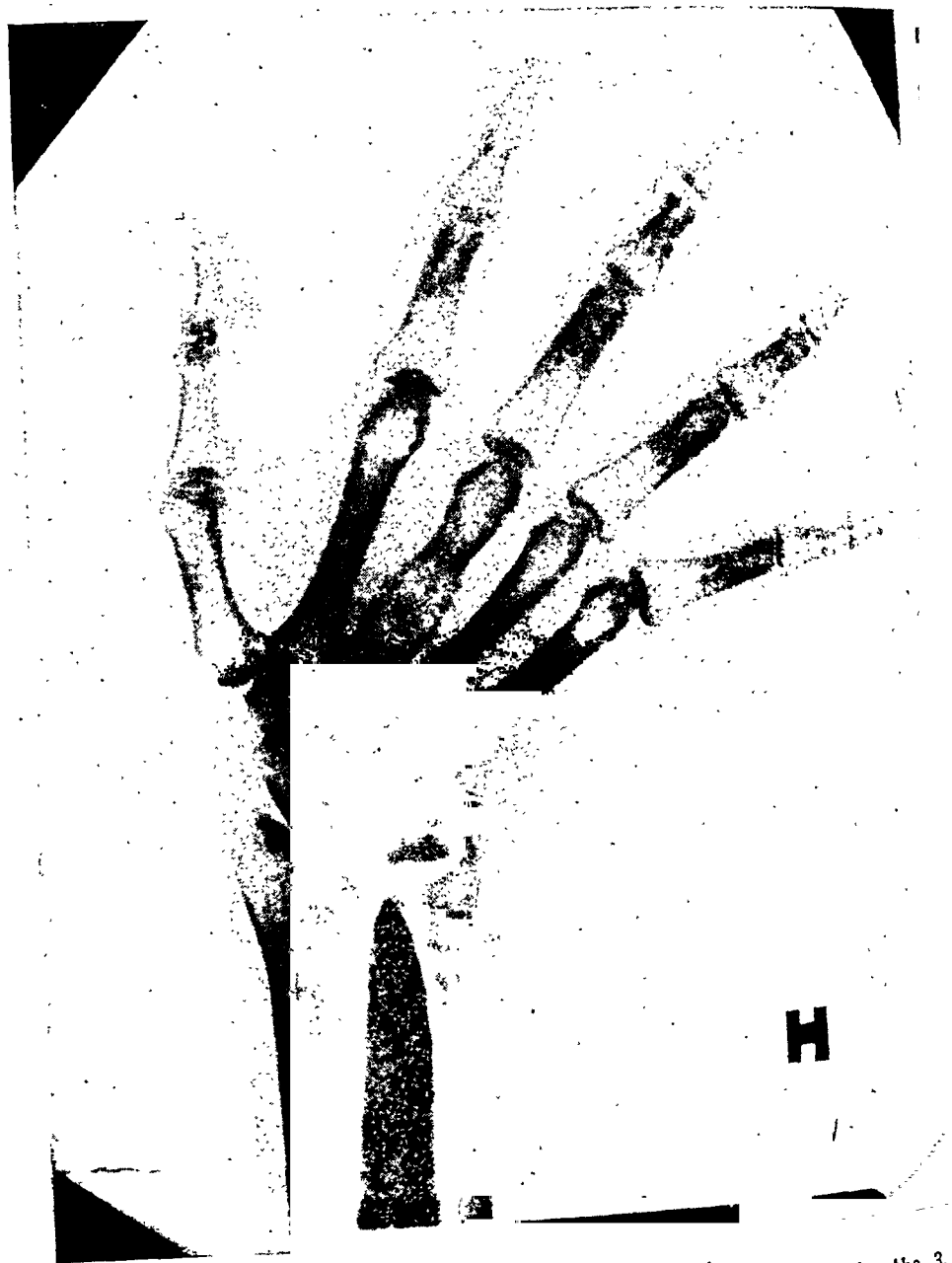


Fig. 5. Note the multiple medullary and subperiosteal cysts in the 3. metacarpal bone.

In local anasthesia after 2 cg morphium, Enucleatio tumoris gland, parathyreoideae was performed.

Ordinary struma incision. Remarkably numerous blood vessels in front of and behind the fascia colli. The fascia was cut, mm. Sterno-thyreoidi and sterno-hyoidei were kept aside and the thyroid gland was inspected.

The observed tumour could be localized to the lower left lobe of the gland. The front of the tumour was covered by a thin layer of thyroid tissue. This layer was removed and bent upwards during the dissection. The tumour itself was covered by a thin capsule, very thin on the front and lateral sides, but more pronounced on the medial and back sides. — During the following dissection the tumour was observed to consist of 2 greater lobes. One of them lying in front of the other, about 2×3 cm, projecting into the jugulum, behind the clavicle. After this tumour had been luxated and lifted up, the next tumour was observed. This tumour was somewhat smaller than the first, more solid than the first and surrounded by a more marked capsule. Its position was behind and at the same level as the midst of the left lobe of the thyroid gland. In the sulcus between those two the recurrent nerve was seen closely adherent to the tumour capsule. — On the fronted and lateral side of the inferior tumour, a nodule about the size of a bean was isolated, probably consisting of thyroid tissue. This was extirpated too, whereafter suturation and glass drain. The patient was in good condition during the operation. The operation lasted $1 \frac{1}{2}$ hour, because of the delicate consistency of the tumour. —

30/1 42: The patient reacted normally after the operation. On the day of the operation he received 10 ml calcinat (10 %) intravenously, and thereafter 1 g calzan in milk 5 times daily. He presented no symptoms of latent or manifest tetania. The signs of Trousseau and Chvostek did not appear at all. He was very hoarse after the operation, but with rapid improvement during the first days of recovery. A mixture containing ammonium chloride was administered to reduce the mucous secretion after the administration of calzan had been stopped. His voice has cleared remarkably but is still hoarse. The wound is practically healed, and he is therefore transferred to the St. Josephs Hospital for further observation.

Laryngoscopic examination before operation:

The left vocal chord is paretic in middle position. Larynx is small of caliber because of a prominent tongue root. The right vocal chord is normal.)

The extirpated tumors were analysed by prosector R. Eker, with the following result: Received a tumor 4.5×3 and 5×2.5 cm. Seems to be clad by a capsule. Tumor is mostly built up of grey, compact and homogeneous tissue, of rather soft consistency. In one corner some cysts filled by colloid-gelatinous masses are observed, varying in size between pin head and a pea. Another specimen received, half size of compact consistency and grey colour. The same is cut up and embedded.

Microscopic examination: In slices from the big tumor one observes a tumor tissue, divided into lobules by broad areas of connective tissue. The tumor tissue is built up of epithel cells, which form closely connected columns mostly with alveolar or palisade grouping of the cells. The cells form some rosettes around capillary vessels, also some lumens are found, some of them rather big and surrounded by multiple layers of cells. The lumens are filled by colloid and isolated, rejected cells and lipid macroph-

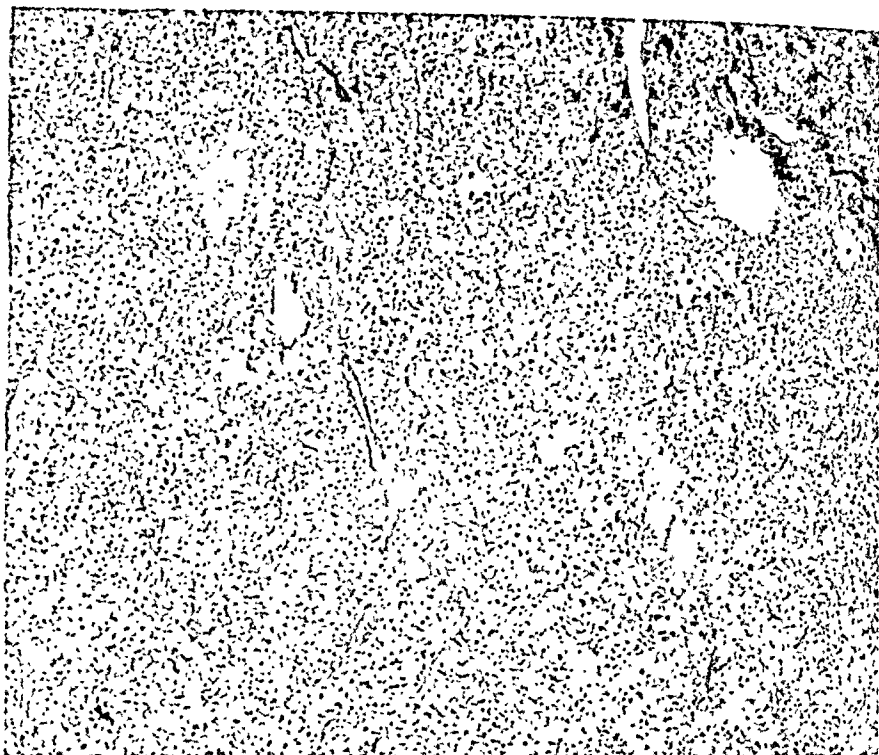


Fig. 6. Photomicrograph of parathyroid tumor. Ocular 7. Objective 10.

ges, probably also crystals of fatty acids. The epithel cells are cubic or polygonal shaped and of varying size. Rather many of them enclose a clear vacuolized cytoplasm with a bladderformed nucleus, rich or middle rich in chromatin, many of them with distinct nucleoles. There is a marked variation in the size of the nucleus, but not in content of chromatin and only a few mitoses are observed. Further a markedly reduced number of cubic cells with eosinophil granulated cytoplasm is found. Between the epithel columns, mince, but richly arteriolized strings of connective tissue are observed. This tissue is middle rich in cells. Most of the vessels are capillaries. The border line between epithel and stroma is mostly sharp, some strings of epithel with indistinct borders are observed between the layers, still one cannot speak of malignant growth. Slices from the small tumor present the same picture. Fat is not observed in the stroma. The same moderate atypical cell formation and somewhat indistinct border line between epithel and stroma is observed. No marked infiltration by leucocytes is observed. The epithel is found projecting into the lumen of one vessel at a certain spot. —

Diagnosis: Adenoma parathyreoideae. Slight atypical cell formation. R. Eker(s). Department of pathology of the Norwegian Radium Hospital. 5/2 42: The patient is still hoarse, the left eye opening is smaller than the right. His condition has improved and he has no pain any longer in the

right elbow or the finger points. The tumor on the back of the right hand can hardly be seen any longer. He complains still of pains in the right thigh and knee. He is allowed to leave hospital today.

3/6 42: The patient presents himself for further control today. He gets tired when walking several kilometers. No marked dyspnea. Right thigh elbow and hand much improved. The tumor on the right hand has practically disappeared. Appetite is good. Increase of weight 10 kg since operation. Still hoarse. His thirst is not pronounced any longer and urine secretion has diminished. He feels fit and is in good spirits, in contrast to the time before operation. Weight today 79.6 kg. Spec. gravity of urines 1010, acid, normal.

Commentary:

Albright, Aub and Bauer (29) distinguish between the following chief types of hp.:

- 1) hp. with symptoms from the skeletal system (cysts, fractures, brown tumors).
- 2) hp. with simple osteoporosis.
- 3) hp. with nephrolithiasis and — or without skeletal symptoms.
- 4) hp. with nephrocalcinosis and impaired renal function.
- 5) acute hp. (until now only presented from experiments on dog.)
- 6) Pseudopaget.

The patient described here presents symptoms from 1) as well as from 4). On the whole, cases with skeletal symptoms are registered as the most frequent. This does not necessarily mean, that skeletal symptoms are present in all cases, so much more as this gives evidence of pathological endocrine changes of long standing. In typical cases, as in the case reported above, the picture starts with pains in the arms, legs or back. So it happens that the case for a long time is registered as a case of lumbago (cf. the case described by Harbitz and myself), ischias or neuralgia. The fact that all therapeutic measures fail to show any result whilst the invalidity of the patient steadily increases, is apt to lead up to the right diagnosis. In more pronounced cases a sudden spontaneous fracture after slight traumata is of good help for the diagnosis. As a matter of fact the pathologic condition has been existing for a long time, often years before these symptoms appear. A future task will therefore be to further the possibilities of early diagnosis. This again will lead to better results of treatment. Doubtful cases of loss of weight, anorexia, constipation, nausea, mental disorders, bone pains, asthenic condition, fever and diminished renal function have to bring into consideration the possibility of hp. and to start the necessary investigations (Ca estimation in blood and urine). The changed calcium metabolism is the key symptom of the disease.

Albright has set up the division of the symptomatology into 3 parts:

- 1) Symptoms which derive from the hypercalcemia per se
- 2) Symptoms which derive from skeletal changes, and
- 3) Symptoms which derive from the raised calcium and phosphorus elimination in the urine.

1) To this group of symptoms belong: nausea, loss of appetite, loss of weight, constipation, vomiting. It is doubtful whether all the symptoms just mentioned are caused by hypercalcemia. Some of them must belong to diminished renal function or acidosis etc. Symptoms as hypotonia, diminished electric irritability and diminished QT interval, belong to the same group.

2) Decalcination and demineralization of the skeletal system in certain cases leads to very characteristic pictures like *ostitis fibrosa Recklinghausen*, in other cases only to the appearance of isolated cysts or *osteoblastomes* and in some cases only to a general *osteoporosis* with all changes from light to severe loss of calcium in the skeletal system.

Opinions are different as to the question, whether the pathologic bone process or the endocrine changes developed by the *parathyroidea adenom* is the primary agens of the disease. Most authors seem to represent the opinion, that the skeletal changes are secondary, indicating an increased resorption, which brings the ossein to be a more marked substance in the bones than normally. The change is a similar one, as is met with in other pathologic conditions which are followed up by increased resorption of bone, for ex. *chronic glomerulonephritis* (Bergstrand) (30).

Bergstrand describes the first stadium of the disease as one where the bones change to be porose, as *osteoclastic* or *osteolytic* processes in the *Haversian channels* and at the same time regeneration of connective tissue are at work. The bone marrow itself has probably not undergone any change at this stage. During the later course of the disease the bone marrow is more and more displaced by loose and vascularized connective tissue. The richness in thinwalled blood vessels gives rise to bleeding with formation of «brown tumors». Resorptive processes in these tumors eventually give rise to formation of cysts. Parallel with resorption of bone, regenerative processes are at work. But the last mentioned bone apposition is so poor, that it cannot overcome the destructive processes.

The demineralisation in hp. is a so marked symptom, that it is natural to assume that the symptoms of hp. will be observed earlier during conditions, where the demand for minerals from the bone system is increased. Such is the case during pregnancy. During the last part of pregnancy, it is calculated that the mother does not retain calcium enough to meet the requirement of the fetus, which actually happens to be the double of the amount retained. In the last trimester of pregnancy conditions are present to accentuate the symptoms of hp. — As hp. happens to occur about 3 times so often in females as in males, there is sufficient reason for gynec-

cologists to give attention to the possibility of this disease, especially in connection with cases of osteomalacy during pregnancy or lactation.

Cases of hp. during pregnancy are already reported. Spingarn and Geist (31) have described one case in a primipara aged 29 in the 4. month of pregnancy. The pregnancy was terminated because it was felt that the combined state of hp. and pregnancy would affect both mother and child unfavorably. The chemical analysis of blood gave from 5 to 5.95 m. equ. Ca before and 7.2 m. equ. after termination of pregnancy, a feature which is worth noticing. On a neutral ash diet containing approximately 100 mg of calcium daily, the patient had a daily average output of 431 mg calcium (normal ca 100 mg daily).

Friderichsen (15) gave the report of one case of high interest in this connection. A child, breastfed during the first 3 months of life and thereafter receiving *allaitement mixte*, at the age of 5 months suddenly developed tetania with a blood calcium value of 3.3 m. equ. in spite of increased calcium content in milk from the mother. The symptoms disappeared 1 ½ month after breast-feeding was stopped and blood calcium returned to a normal level. Examination of the mother led to the diagnosis of hp. The chemical analysis of blood gave 8.2 m. equ. Ca and further typical changes were found in the skeletal system. An adenoma in the parathyroid glands was extirpated at the following operation. In this case hp. must have been present during pregnancy already.

Hp. is not seldom accompanied by anemia probably caused by changes inflicted upon the bone marrow by the condition of hp. The anemia in my first case was normochrom, in the here presented case hypochrom. —

3) The increased calcium and phosphorus excretion through the kidneys is accompanied by morphological changes in the kidneys. Calcium deposits can be observed in the tubuli and in the glomeruli as well. The distal part of the tubular system however, is the part where calcium deposits are chiefly localized, probably because the urine is concentrated here, which prevents a certain part of the calcium from remaining in solution. — The renal function is reduced by the calcium deposits, and this again causes retention of calcium in the blood, when the kidneys can't manage to excrete their part. Theoretically one has to assume that hp. in its early stadium cannot be diagnosed or excluded by blood calcium determination alone. There remains the possibility of hp. in spite of normal blood calcium level, when the output of calcium in the urine surpasses the normal limit, with marked negative calcium balance as a result. The question rises, whether or not an increased amount of parathormone in blood can bring about a hypercalcemia as long as the renal function is normal. From experiments on dogs it is well known that the injection of hormone causes marked hypercalcemia, so that this fact is used for standardization of parathyroid preparations (Collip). It has to be remembered however, that the dosis in question is rather big and that renal function is disturbed until complete cessation of urine excretion. —

Calcium is probably concentrated very little in the kidneys during its passage. Until now our knowledge of this problem is scanty. Only the ioniz-

ed part of blood calcium is supposed to pass the kidneys. A threshold for calcium seems not to exist, and taking into account that calcium leaves the kidneys in a concentration about the double of the ionized blood calcium, one may suppose, that the index of concentration lies between 1 and 2. A marked rise of calcium flow to the kidneys can therefore be eliminated only by a rise of water diuresis. This seems to be the explanation of polydipsia and polyuria, distinguished symptoms of the disorder. —

The serum calcium is present in 3 forms: a minor part is physically dissolved, another undissolved part is bound to serumprotein [Salvesen, Linder (32)] and the last part is kept in solution by the protracted sedimentation which characterizes oversaturated solutions of calcium-carbonate or phosphate. The amount of ionized calcium can be calculated, when the amount of serum protein and total calcium are known (Mc. Lean & Hastings) (33) there being an equilibrium between calcium and protein, which may be expressed according to mass law equation:

$$\frac{\text{Ca} \cdot \text{protein}}{\text{Ca-proteinate}} \cdot K 10^{\div 2.22} \text{ (tp } 25^{\circ} \text{C, pH 7.35)}$$

When the kidneys can eliminate the surplus of calcium no longer, blood calcium will consequently rise proportionally to the reduction of kidney function. As long as the renal function is adequate, the calcium elimination through the kidneys is abnormally high. (In my first case 5 times as great as normal and in the case presented here 8 times a great). When the renal excretion of calcium is lowered, the amount of calcium in the stools can rise, as stated by Albright, Baird, Cope and Bloomberg (35).

Under physiological conditions there seems to be a constant relation between serum calcium and phosphorus (Howland), the product of both expressed in mg per cent is 40 (10×4). Generally serum phosphorus is lowered in hp., when serum calcium is raised and the output of phosphorus in the urines is greater than normal. When kidney function diminishes, however, also serum phosphorus can rise to a higher level, as was stated in the case presented here. The effect of this again is a tendency to lower serum calcium, but the regulation of the relation between serum calcium and phosphorus does not function as under physiological conditions. In the case presented here serum calcium as well as serum phosphorus were distinctly high ($\text{Ca} \times \text{P} = 88$), in the case of Schrumpf and Harbitz diminished: $\text{Ca} \times \text{P} = 22$, (blood calcium was very high, but serum phosphorus was low.) Actually it is not the simple product which is of importance, but the product of ionized calcium and phosphorus. The discrepancies may therefore theoretically be explained supposing that variable amounts of calcium are ionized: Acidosis will augment and alkalosis diminish the quantity of ionized calcium. Nevertheless, the contradictory results quoted above can hardly be explained in this way, there being a significant acidosis in the case with a high calcium phosphorus product.

Some cases of hp. present hypocalcemia, hypophosphatemia and dimi-

nished calcium excretion. Impaired kidney function is accompanied by phosphate retention and this again reduces the serum calcium level. Such a case was published by Downs and Scott (34), concerning a 58 year old male with renal colics, calcium atrophy of the bone system and multiple calcium deposits in both kidneys. Serum calcium was only 3.75 m. equ., but serum phosphorus was high. The autopsy confirmed the diagnosis. There was found an adenoma in one gland and hyperplastic conditions in the three other parathyroid glands. — A constant relation between serum calcium and phosphorus does consequently not exist in hp., probably because of the disturbed kidney function, which is present in most cases. —

In this connection it can be of importance to point out the presence of acidosis in the case presented by me, so much more as this feature has not been observed in the literature as far as I have seen, with the exception of one case presented by prof. Carnot and dr. Lafite (36) at the March meeting 1938 of the Société Médical des hôpitaux of Paris. In this case there was a slight diminution of the alkali reserve of the blood. The laboratory findings demonstrate (see diagram and tab. 1), that with exception of 2 days (14/1 and 16/1), there was a marked reduction of the alkali reserve — before as well as after the operation. The alkali reserve was generally reduced to about one half of the physiological value, which is 26 m. equ. (found as the middle value on 100 healthy persons). There remains to explain this acidosis. From experiments on animals it is known, that injection of big parathormon doses does cause hypercalcemia and hypercalcuria and thereupon azotemia, convulsions, vomiting and sudden death. In my own case the amount of phosphates in blood was markedly increased (5.4 mg %) and the total base (determined electrolytically after the method of Herman Nielsen (37) in blood) showed on some days values well below normal, especially on the 3. and 5. day after operation there was a marked drop in total base — still a regular, convincing correspondance between the acidosis and reduction of total base is missed. The compelling logic is to suppose that the acidosis is established partly as the consequence of (1) abnormous loss of base in the urine (2) or retention of acid equivalents, particularly phosphates (3) or diminished production of ammonia in the kidneys. On the basis of previous experimental results on animal already described, it seems justified to conclude, that the acidosis is brought about as a direct effect of the hormone upon the body. We know that as a result of diminished h-jon concentration the ionization of calcium is raised. As moreover the parathyreoid glands regulate the ionized part of blood calcium it lies near to hand to suppose, that the acidosis is part of a mechanism which tends to mobilize transport and eliminate as much calcium as possible. If so is, it must be expected, that the acidosis will disappear as soon as the adenoma has been successfully removed by operation. But this was not the case here. The acidosis persists still 14 days after operation.

Another possibility is to register the acidosis as a renal acidosis. An increased elimination of bases during a long period, combined with retention of acid equivalents and diminished ammonia production in the kidneys

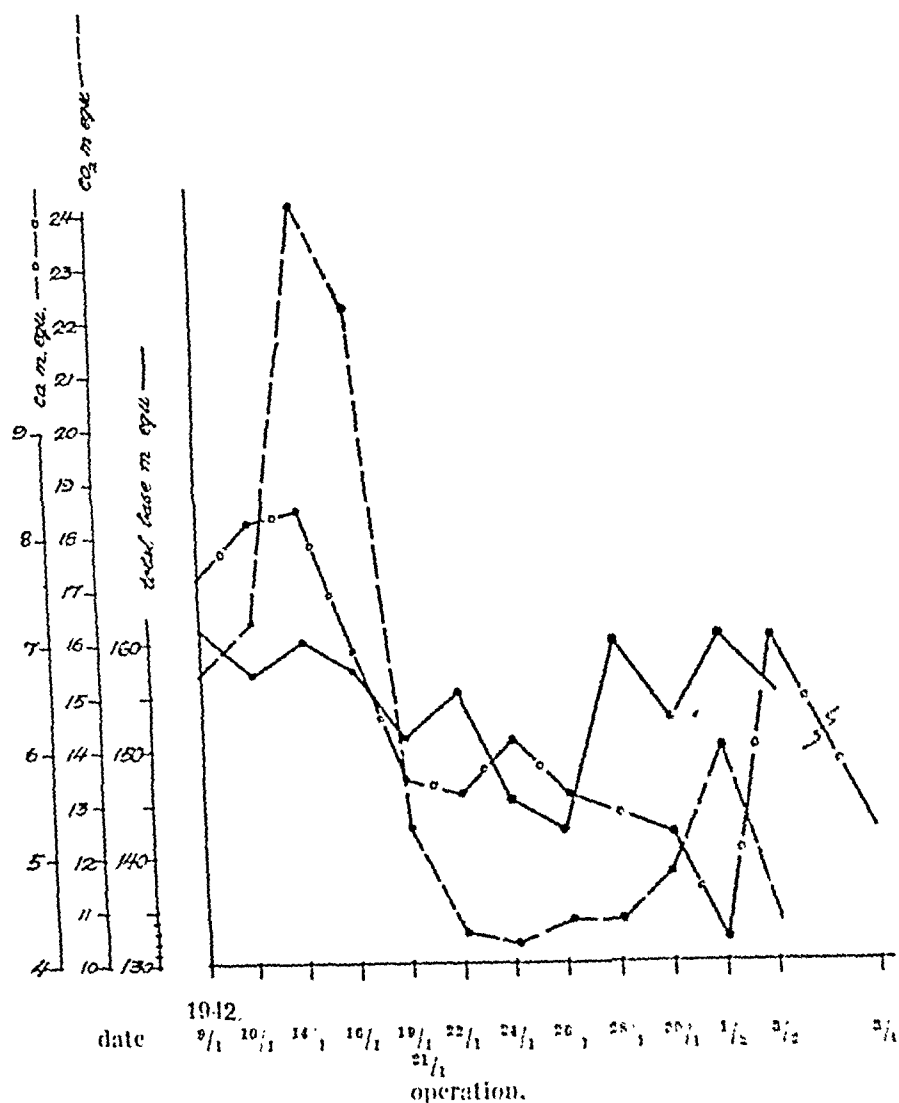
Table nr. 1.

Total base, alkalireserve, calcium and phosphate in serum before and after operation.

Date	total base	CO ₂ m. equ.	Ca m. equ.	phosphate mg %
9/1	161	15.4	7.6	5.4
10/1	157	16.3	8.1	
14/1	160	24	8.2	
16/1	157	22	6.9	
19/1	151	12.6	5.7	
21/1 operation				
22/1	155	10.6	5.6	
24/1	145	10.4	6.1	
26/1	142	10.8	5.6	
28/1	160	10.8		
30/1	152	11.7	5.2	
1/2	160	14	4.2	
3/2	155	10.8	7	
3/6	4 months after operation:		5.2	

tends to produce a gradually increasing acidosis. If so is, it is easily understood that the acidosis will last in spite of successful operation. For it is to be expected that some time will pass before the renal function is improved, the ammonia production increased and the mineral reserve of the body restored. This theory is to my opinion the most probable, as is strongly suggested by the output of base given in detail later in this article. As a result of depletion of calcium and phosphorus through the kidneys intrarenal calcium deposits will be found, as well in the cortical region as in the pyramids in some cases, while in other cases the kidneys are little damaged. Eventually stones will be found in the renal pelvis or the bladder, often combined with secondary infection. When the disorder is diagnosed early, the calcium deposits in the kidneys can be absorbed after successful removal of the parathyroid adenom, whereafter the renal function is ameliorated. If the impairment of the kidneys is too marked, the situation of the patient will slowly be aggravated, and death will issue as a cause of reduced renal function. —

American workers have contributed much to our knowledge about the relative frequency of urinary lithiasis in hp. In Castleman & Mallorys (38) material from Boston consisting of 25 cases, ostitis fibrosa was the single symptom in 5 cases, nephrolithiasis alone in 11 cases and ostitis fibrosa combined with renal calculi in 9 cases. The same authors have collected 119 cases from the literature, where ostitis fibrosa was present in 70 cases (59 %), renal calculi alone in 3 cases (2 ½ %) and both symptoms in 46 cases (38.5 %). Albright, Fuller, Baird, Cope, Oliver & Bloomberg (39)



report, that 27 % of 83 cases had renal calculi. Barney & Meintz (40) report 18 cases of hp. with renal calculi in 11 cases. The youngest patient was aged 13, the eldest 62 years. Skeletal changes were present in 12 cases. In 6 cases renal calculi and bone affection were both observed. Bilateral renal calculi were found in 4 of 11 cases. The authors state that hp. causes renal calculi in 4—5 %. —Griffin, Osterberg & Braasch (41) report the incidence of hp. in the Mayo Clinic material to be less than 0.2 % of cases with renal calculi. In the Cleveland clinic the frequency of hp. amongst cases of renal calculi is stated to be 0.1 %. From Norway Brodersen (42) in 1935 reported 15 cases of renal calculi, which were examined for clinical evidence of hp. No case of hp. was found.

In the case reported above by me no sign of renal lithiasis was found. The x-ray examination of the kidneys however showed so marked kidney

Table nr. 2.

Output of totalbases and calcium in urine before and after operation.

Date	Diuresis	spec. gravity	totalbases m. equ.	calcium m. equ.
16/1	2.2 l	1.011	462	112
17/1	2.5 l	1.010	475	380
18/1	2.4 l	1.005	324	161
19/1	2.8 l	1.012	750	350
20/1	2.6 l	1.009	429	281
operation				
23/1				
24/1	1.2	1.008	108	21
25/1				
26/1	1.35	1.005	90	19
27/1	1.2	1.015	300	24
28/1	1.6	1.005	120	107
29/1	1.5	1.013	405	121
30/1	1.65	1.003	398	63
4/2	2	1.010	490	56
5/2	1.8			52
6/2	2.15	1.030		49

shadows, that it is only logic to suppose the kidneys contained an increase amount of calcium. It does not surprise that the renal function under these circumstances was diminished (max. urea clearance 14). Like Holtens (17) statement in his case, the concentration power of the kidneys was most affected. The specific gravity of the urine was never higher than 1.011 before operation, with variations between 1.002 and 1.011. After the operation the specific gravity rose to 1.030, which signifies a rather rapid recover of the renal concentration power. As a consequence of the diminished renal function, azotemia was found amounting to 75 mg % blood urea. Only traces of albumin were observed and in the urine and only a few lymphocytes in the sediment. It seems to be a characteristic feature in such cases of hp. that only traces of albumin or no albumin at all are found, in contrast to diminished renal function. The same fact was observed in another case described by Schrumpf & Harbitz. —

In addition to the calcium elimination, the output of total bases in the urines was controlled before and after operation. The results are presented in table nr. 2.

It will be noticed that there was a marked output of total bases before the operation, with variations between 324 and 750 milliequivalents. After the operation there was first a reduction in the output of total bases (90 m. eq.); thereafter increased values were found, averaging somewhat lower values than before operation (300—490 m. equ.). The differences between

is discussed. Reference is made to the calcium-phosphorus product, which was abnormally high, probably because of the disturbed kidney function.

The alkalireserve, the calcium and total base in serum and the elimination of total base and calcium in the urine are quoted, as well during the period before as after successful operation. The necessity of repeated calcium analyses in serum and the urine is inopted out.

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Tuberculin and environment investigation of schoolchildren.

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In Bergen, as elsewhere, the tuberculosis mortality and morbidity show a continuous decline. Fig. 1 shows this decline in Bergen, Trondheim, and Copenhagen during the most recent years. Stockholm is not included in this comparison as its tuberculosis decline runs approximately parallel with that of Oslo. The lines, based on the annual reports of the public health services of the respective cities, are drafted so as to represent the average for periods of three successive years.

Fig. 1 shows an interesting phenomenon, i. e. the difference between the tuberculosis mortality and morbidity. The *mortality* shows a constant and uniform decline, particularly after the World War 1914—1918. This decline runs approximately parallel in the three Norwegian towns. This result is presumably due to improved hygiene and treatment, the expansion of treatment centres and earlier diagnoses. As was to be expected, Copenhagen, with its well-developed diagnostic and therapeutic machinery, shows the lowest figures.

One might expect the frequency of infection and the morbidity to show the same uniform decline. But this is not the case. As for the *frequency of infection*, statistics concerning tuberculin-positive

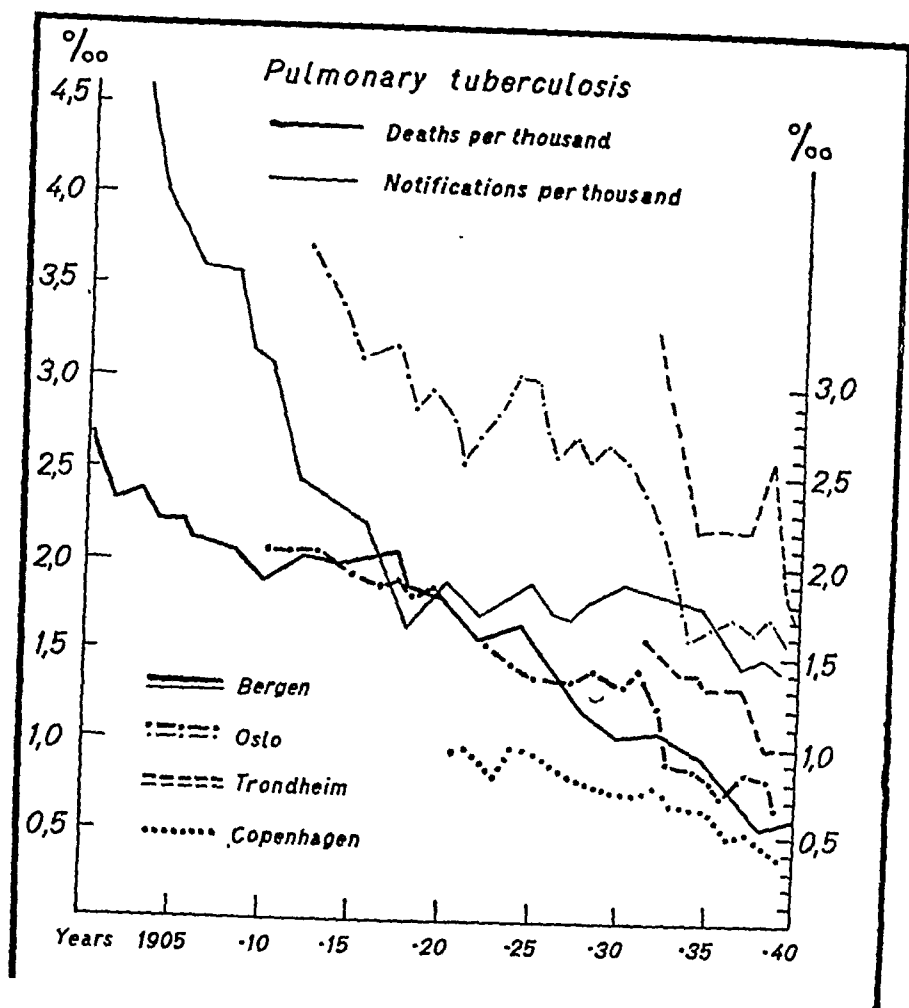


Fig. 1. Mortality and morbidity curves for pulmonary tuberculosis in the three largest towns in Norway and in Copenhagen. Data from annual Public Health Reports.

persons in the larger towns show that it continues to be between 80 and 100 per cent. in adult life. All that has happened is an upward displacement of the age on infection, from childhood to adolescence.

As for the tuberculosis *morbidity*, a striking phenomenon is to be observed in the curve both for Bergen and Oslo. After a marked decline at the beginning of the century, there is a remarkable stagnation in the morbidity from the beginning of the second decade; it is not overcome till the last ten years. Even Copenhagen, with its low mortality, shows approximately the same figures as Bergen for notified cases of pulmonary tuberculosis in the last few years,

—1.7—1.5—1.4 per 1000 in the period 1937—1939 (not included in fig. 1). This stagnation in the decline of the morbidity cannot be traced solely to intensified anti-tuberculosis work having led to the discovery of more cases. There must be another reason for the obstinacy shown by the morbidity.

Once infection has taken place, the chances of the development of disease can in the main depend on two factors, — the resistance of the individual and his exposure to infection. How much each of these two factors determines the tuberculosis fate of the individual, and what are the intrinsic and extraneous stimuli influencing the variations in resistance are some of the most important problems of tuberculosis research today.

Broadly speaking, the first decline in the morbidity can in the main be traced to the increased resistance conferred on the community by the great progress made by hygiene in all directions. The more frequent isolation of open sources of infection has been beneficial in a lesser degree. The stagnation also shows, broadly speaking, that a further decline in the tuberculosis morbidity by these means is not to be hoped for, and that we must concentrate more on overcoming the other factor, i. e. the exposure to infection. Disease can develop only after infection, and the chances of infection leading to disease grow, in the opinion of many, with the frequency of contacts with infectious cases.

In acknowledgement of this view, there has been a gradual change in the epidemiological direction of the anti-tuberculosis campaign, with continuous intensification of the search for infectious cases. The great slogan in the beginning of the diagnostic centre era is environment investigation. This change of direction in the tuberculosis campaign may perhaps partially account for the new decline in the morbidity which occurred in the third decade of this century, and which is very marked in Oslo at any rate. This search for sources of infection has been further aided in Norway by an addition to the tuberculosis law of March 1942 which requires the notification of *all* manifestations of tuberculosis, not only the most infectious, and compulsory environment examinations centring about them.

This procedure can hardly reduce the morbidity below a certain low level. Bachmann, among others, insists that the whole of this system hinges on persons who are already infected or who are

infectious. In either case, such infection may have done great harm, but the extent of such harm cannot always be determined by a single environment examination. In urban communities in particular, the examination is not extended to all who are infected, and it is seldom that one can be sure that a positive tuberculin reaction is due to a recent infection. It is thus impossible to keep under supervision persons who have recently become positive reactors and who, during the next few years after infection, are most liable to fall ill. Such an environment examination can therefore not be effective unless it is repeated at intervals of months and years, and this would require a too cumbersome machinery.

If our aim is to root tuberculosis completely out of a community, we must *prevent* infection, not only *arrest* spread of infection at a given moment.

A significant step in this direction is screen-photography — the miniature Röntgenogram — which enables one to satisfy the constantly growing demand for a radiological examination of the whole community, irrespective of environment and known sources of infection. A complete annual examination would in a few years overcome tuberculosis in a community, but even the failure of a small fraction to undergo examination would lead to shirking of this test by a comparatively numerous group of patients.

In the first place, experience has shown that failure to appear for examination is most marked in the lowest social ranks of the community in which tuberculosis is most prevalent. In the second place, those who suspect themselves of being ill will be those who most dread such an examination on account of the economic loss tuberculosis entails and the stigma still attached by the community to one who has been marked as ailing. The above presupposes a voluntary examination, and this should be the solution of the problem as far as possible.

In 1941, H. Chr. Olsen wrote: »Had the Bornholm investigation been carried out by force, it had not left in the community that comprehension which is the the best guarantee for the future.» As the tuberculosis campaign must be far-sighted and inclusive of all ranks in the community, its goodwill and sympathy are required in a marked degree everywhere.

Miniature Röntgenograms — screen-photography — cannot alone solve those problems of tuberculosis research in which it is of

importance to ascertain the date of a first infection. Among other questions are those concerning the length of the interval between infection and disease, the influence of age at the time of infection on the subsequent course of the disease, the importance of re-infection and superinfection as compared with primary infection, the tuberculosis-prognosis for the tuberculin-positive versus the tuberculin-negative, and the conditions under which tuberculin allergy varies or ceases.

It is possible that in a few years BCG vaccination will, to a certain extent, make these questions superfluous. But at any rate today they are burning enough to judge by the keenness with which they are discussed. We must be able to answer them, are we to agree as to the course the tuberculosis campaign is to take in the future.

It is primarily these questions which have created a demand for a tuberculin register which will, besides, prove useful in combating infection in association with other methods. Such a register must be based on an annual tuberculin examination of the whole community, from the school age to 35.

According to Ustvedt, 70—80 per cent. of all the infections in Norway occur within these ages. According to the Health Service data, 75 per cent. of all the morbidity is to be found within the same limits. In 1941, Bachmann wrote: »Parallel mit der Schirmbilduntersuchung müsste an Hand von Pirquetkatastern, die von der Schulentlassung mindestens bis zum 25. Altersjahr fortzuführen wären, der progressive Grad der Durchseuchung festgestellt werden.»

Malmros and Hedwall strongly urge the tuberculin examination of the whole of the Swedish nation, particularly with a view to ascertaining the date of a primary infection.

In 1939, the Norwegian National Association against Tuberculosis had this register on its programme (Hertzberg) and in certain places it is already introduced.

The prophylaxis of tuberculosis should therefore today consist of several co-operative measures — environment research, screen-photography, a tuberculin register, BCG vaccination, and perhaps also propaganda and popular education in a category by themselves. It is particularly at the present time that this work must be intensified as much as possible, for the war creates conditions

favouring a rise in the tuberculosis morbidity through reduced resistance and the opportunities for environmental changes due to evacuations etc.

When the diagnosis station in Bergen was expanded in 1941, more attention was naturally paid to these tasks. The station's accommodation and the state of affairs at that time did not permit of the introduction of a tuberculin register. In compiling it, the medical examination of schoolchildren is an important step, for it often forms the foundation on which a register is further built up, as was the case with the Bornholm community examination in 1935—1940 (H. Chr. Olsen).

For several years and in many different places tuberculin examinations of schoolchildren have been carried out. No great preliminary work or expense is required for these examinations which are easily carried out with almost 100 per cent. effect. The part they play in the campaign against tuberculosis is not always obvious. Tuberculosis at school age is characterized by primary infections nearly always running a benign course and with an insignificant risk of infection. An examination limited to schoolchildren is therefore of little significance in combating infection. It is only when this work is extended, so as to include *environment investigations* centring about the tuberculin-positive, that it becomes valuable. The prospects of discovering a source of infection are excellent when the interval after infection is relatively short and the environment is stationary as is usually the case.

This examination gives a welcome opportunity to investigate asocial environments and to check up already known sources of infection. An annual examination induces both children and parents to take an interest in the tuberculin test and tuberculosis work; and a start has been made towards an extension of the examinations to the much more significant years of adolescence.

These environment investigations centring around *all* tuberculin-positive schoolchildren should be an obvious sequel to the medical examination of schoolchildren, but it is only in the most recent years that they have been carried out on any extensive scale. No such comprehensive school medical examinations have hitherto been carried out in the larger towns in Norway.

It was not difficult to carry out such an investigation in the autumn of 1941 in Bergen, with its 100,000 inhabitants and some

12,000 schoolchildren, — figures modest enough to allow of a comprehensive survey of the whole situation. The provision in the summer of 1941 of the screen-photography apparatus had solved the difficulties with the tedious radiological work, and the tuberculosis station of the Health Service had in recent years been so well developed that there were good prospects of most of the sources of infection being discovered. The investigation followed two lines:

1. The tuberculin examinations and
2. Environment examinations.

1. *The tuberculin examinations* were merely a further development of the already existing tuberculosis work among schoolchildren which consists of:

- A. Tuberculin testing,
- B. Radiological control of all the tuberculin-positive, and
- C. BCG vaccination of the tuberculin-negative at the school-leaving age.

A. *Tuberculin testing.* A 1 cm long scratch is made on the volar aspect of the left forearm through a drop of tuberculin applied to it. The skin is dried after 5 minutes and examined 48 to 72 hours later. The slightest positive reaction is a 4 mm infiltration. Smaller infiltrations are subsequently controlled by Mantoux 1/10 mg. The Pirquet-negative are not subjected to any further tuberculin test. The same person carries out the tests and reads off the reactions, — a point of great importance if uniform results are to be achieved, for in spite of all the rules and definitions, the estimate of a Pirquet reaction is always liable to subjective bias.

I would like to remark that doctors should agree on always carrying out a tuberculin test in the same position, for example the volar aspect of the left forearm. A positive tuberculin reaction often remains visible for several months, and in this way one often avoids repeating the test.

Koch's old tuberculin, as used by the Health Service, was employed. Elsewhere, Norwegian tuberculin, from the Veterinary Institute, has often been used. During the medical examination of schoolchildren, the German (T) and the Norwegian (N) tuberculins were compared on 114 scholars chosen at random (table 1). The infiltrations were alike in 44 per cent. In 39 per cent. the T infiltrations were larger than the N infiltrations, both reactions being regarded as positive. In 9 per cent. one or other of the

Table 1.
Comparison of tuberculin tests.

	Number of persons examined	114
1.	Infiltration T = Infiltration N	50 (44 %)
2.	" T > N, both > 4 mm	44 (39 %)
3.	" N > T, " > 4 mm	2
4.	" T > 4 mm. N < 4 mm	8
5.	" N > 4 mm T < 4 mm	2
6.	" T & N < 4 mm., Mantoux +	4
7.	" " " " 4 " " 0	4

Re. 2. Average infiltration T = 8 mm., N = 5.9 mm.

" 4.	T in mm.: 10 8 7 5 4 4 4 4	} Failure with N: 2
	N " " : 0 3 0 3 3 3 2 2	
" 5.	T " " : 2 0	} Failure with T: 1
	N " " : 4 4	
" 6.	T " " : 3 2 3 3	} Failure with N: 2
	N " " : 3 2 0 0	
" 7.	T " " : 3 2 2 3	} Failure with N: 2
	N " " : 3 2 0 0	

Failure with the tuberculin test: T: 1 & N: 6

Legends: T = Koch's old tuberculin.

N = Tuberculin from Norwegian Veterinary Institute.

reactions was doubtful or negative, and in 7 per cent. both were doubtful. On the whole, the T reactions were the more definite of the two. The N reaction failed in four cases, the T reaction only in one.

Point 7 shows how important it is to put the lower limit of a positive Pirquet at 4 mm. We see how a more definite and strong reaction is provoked by the German as compared with the Norwegian tuberculin. I should mention that Mantoux's test was carried out with 1/10 mg of Norwegian tuberculin, and that the investigation did not fulfill scientific requirements, for the tuberculin first to be used was the German, and it is possible that an unintentionally stronger and deeper scratch may have been made at the first test, and this may in part account for the difference. Besides, the testing was hurried, and the time taken for drying was not checked up. Yet the difference between the two tests was so marked that in mass investigations it is advisable to state what tuberculin is used in order to ensure uniformity for comparison.

The Pirquet test was carried out only once, without Mantoux control of the tuberculin-negative. The behaviour of the Pirquet

and Mantoux tests, compared the one with the other, seems to vary in the different communities. Thus among Oslo inhabitants born in this city, Hertzberg found the Pirquet test to be defective in 5 to 6 per cent., whereas it was so in about 22 per cent. among the inhabitants of Oslo who had migrated to it. He ascribes this difference in the sensitiveness of the Pirquet test to the relatively great allergy conferred on an urban community by repeated super-infections.

Investigations in Copenhagen (Holm and Ustvedt), Höyanger (Andenäs), and Västerbotten (Wählin) show considerably greater defections of the Pirquet test, from 25 to 40 per cent. The environment in these investigations being less infected than in the case of Oslo, these figures give support to Hertzberg's theory. No such investigation has been undertaken in Bergen, but fig. 1 warrants the assumption that conditions here are much the same as those in Oslo. As for the medical examination of schoolchildren, the fallibility of the Pirquet test is of small account in view of the increased work that would be necessary were the Pirquet-negative to be subjected to Mantoux control. As matters were arranged, the Pirquet examination of each school, with up to 2000 scholars, could be completed in one day, and that of all the national schools in about a fortnight. A Mantoux control would have prolonged the investigation over several months. Besides, this voluntary examination would, by the Mantoux test which is more alarming for schoolchildren, have lost its popularity, and its prospects would have been compromised.

Nor do the Pirquet-negative, Mantoux-positive schoolchildren play any important part in such a study. It is very rare to find active tuberculosis with a negative Pirquet at the school age, and there is little chance of one's finding infected, Pirquet-negative children in a tuberculous environment.

The results of the Pirquet examinations are seen in table 2. A distinction is made between public and other schools. In the public schools, education is compulsory for seven years for all children from 7 to 13. There is also a voluntary, eighth class in these schools. The other schools are the »middel schools», the »gymnasium», the occupational or industrial schools etc. In this as well as in the following tables, the already BCG-vaccinated children are included among the Pirquet-negative when the percentage of the

Table 2.

The school medical examinations in autumn 1941.

	Public schools	Other schools	Total
Number of scholars	8892	2492	11384
Absentees	139	52	191
Percentage of absentees	1.6	2.4	1.7
Refused Pirquet	52	6	58
Earlier BCG vaccinated	209	121	330
Pirquet-positive	854	436	1290
» » percentage	9.8	17.9	11.6
» » negative	7638	1877	9915

Percentage of Pirquet-pos. in the seven classes of the public schools: 9.5.

Table 3.

Results of the school medical examinations in autumn 1941. Grouped by classes.

	Number	Absentees %	Pirquet pos.	Pirquet pos. %
1. class	1176	2.5	74	6.4
2. »	1072	2.5	75	7.2
3. »	1238	1.3	100	8.2
4. »	1236	1.7	101	8.5
5. »	1308	1.7	130	10.2
6. »	1249	1.2	137	11.1
7. »	1237	0.3	179	14.5
8. »	376	1.3	59	16.2
1. »Middel-school»	563	1.8	72	13.1
2. » »	498	3.0	72	14.9
3. » »	515	1.6	103	20.3
1. »Gymnasium»	269	1.5	46	17.4
2. »	178	2.2	37	21.4
3. »	204	5.4	52	26.9
Public School	8892	1.6	854	9.8
»Middel-school»	1576	2.1	247	16.1
»Gymnasium»	651	2.9	135	21.4
Total	11119	1.7	1236	11.4

Pirquet-positive is calculated. It would have been more strictly correct to divide the vaccinated children between probably positive and negative, according to the number of those who changed in

this respect from year to year. But the number of vaccinated children is so small that this procedure would not have affected the results. The figure 9.5 is the percentage of positive reactors in the seven classes of the public schools.

Table 3 shows the results of the investigation in each class, and fig. 2 shows the same in graphs. There was no difference between boys and girls in the public schools. The difference in the eighth class and first «middel-school» may be interpreted as a puberty phenomenon — Pirquet-positive girls of 14 leading, while Pirquet-positive boys do so at 15. For the eighth class, however, the difference is within the statistical standard error.

In the first «middel-school», school conditions have assuredly had a greater influence on the percentage. The curve for the seven classes of the public schools gives a correct picture of the population, and the age-grouping follows fairly closely the class-grouping, — seven years for the children in the first class, 13 years for those in the seventh. The curve for the other classes represents a selected material of less statistical value. In the first place these classes both in the «middelschool» and the «gymnasium», contain scholars belonging to two or more years because of the interposed, voluntary eighth class. The percentage of positive reactors should therefore be calculated according to their age, as is done in fig. 2 to the right. In the second place, only some 40 per cent. of the scholars in the public schools move up into the «middel-school», and only some 50 per cent. from this school go on to the «gymnasium» (see the uppermost curve). These belong to the social upper classes in which the percentage of positive reactors is presumably lowest. Thus the whole curve acquires an artificial downward slant. This sorting out finds expression on the «class-curve» in a kink at the transition to the «middel-school» and «gymnasium». On the «age-curve», the first kink is straightened out at the interposed eighth class, the second kink remains standing.

It would be interesting to learn to what extent this sorting out occurs in relation to the percentage of positive reactors in the various parts of the town. In this connexion, those who were called up for compulsory civil service in February 1942 were asked if they had been Pirquet-tested in 1941, i. e. when they were 19 years old. Fig. 4 A is a chart of Bergen showing how many per cent. of

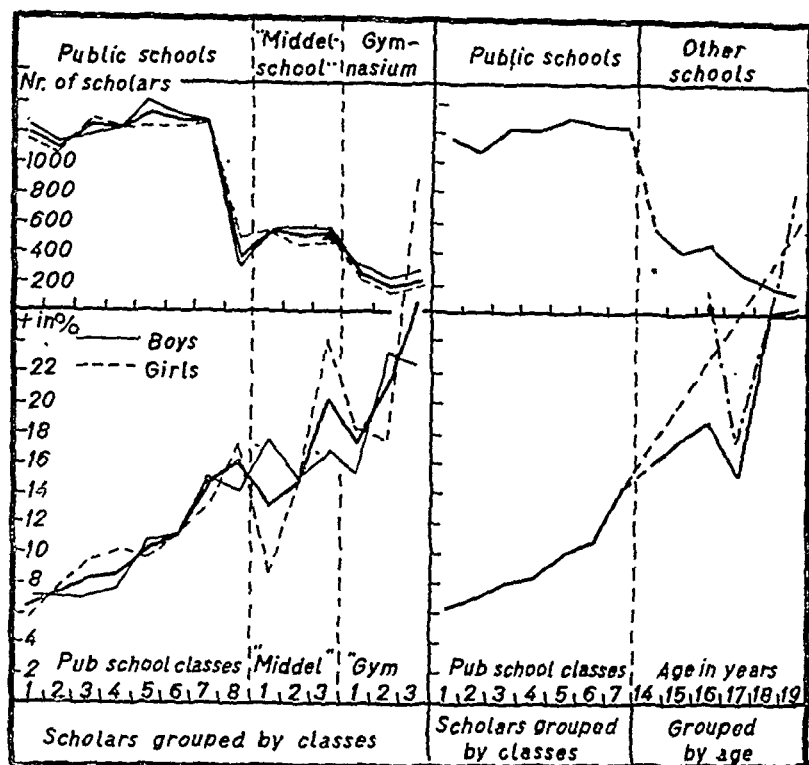


Fig. 2. The findings of the Pirquet examination, grouped according to class and age. The upper curve = the number of scholars. The lower curve = the percentage of Pirquet-positive.

each muster reporting for service were tested with tuberculin. For the purpose of comparison, a chart shows the percentage of positive reactors among the scholars of the public schools in the various school districts. Military muster districts and school districts are not, to be sure, identical, but it will be seen that in those areas in which more than half of the men liable to service had been Pirquet-tested, the percentage of positive reactors among children is under 8, whereas it is, on the whole, over 10 in the areas in which between 25 and 10 per cent. of such men have been tested.

The percentage of positive reactors among the Pirquet-tested men liable to service was 28, — and this tallies well with the 26.4 per cent. for the school-tested persons reaching the age of 19.

It is possible only to guess at the course of the curve for the whole population between the ages of 14 and 19 (fig. 2).

It may be noted that the percentage of positive reactors in the public preparatory schools for artisans is indicated by the stippled

line. These schools represent a worse environment than the higher schools, and their scholars are only about 10 per cent. of the total. In the first half of 1942, 36 per cent. of the 20-year old men in the compulsory civil service were Pirquet-positive. When these figures are compared, a »probable curve», indicated by the dotted line, may be drawn with an abrupt rise in the percentage of positive reactors after leaving the public schools. If this curve represents the

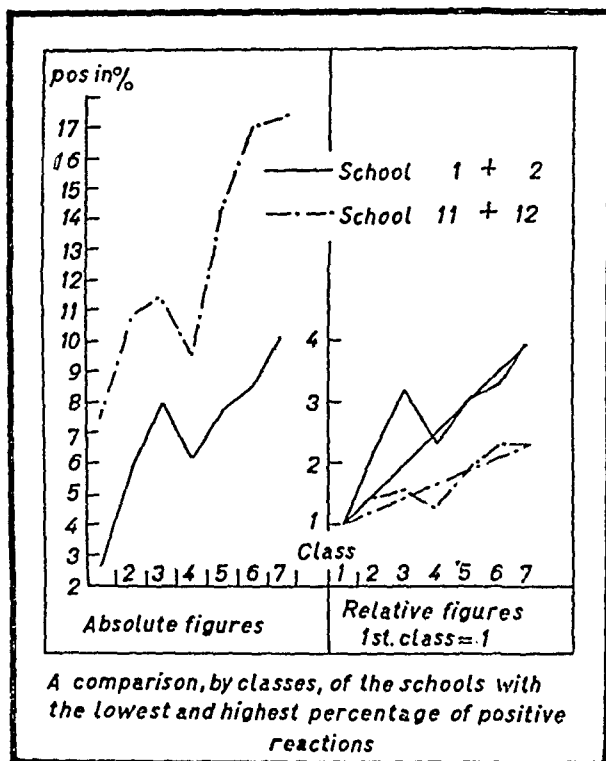


Fig. 3. A comparison, by classes, of the schools with the lowest and the highest percentage of positive reactions.

truth approximately, it justifies the energetic agitation for BCG vaccination among scholars on leaving the public schools.

The next part of the investigation concerns the distribution of Pirquet-positive children in schools and town districts. To ensure uniformity, only the children in the seven public school classes were examined. Table 4 shows their distribution in schools. Schools 1 and 2 show approximately the same percentage of positive reactors as the second class of the public schools. Schools 11 and 12 show a percentage between the sixth and seventh class. The difference between these two groups of schools is greater than three

Table 4.

The seven classes of the public schools grouped according to the percentage of Pirquet positive reactors.

Schools	Number	Pirquet pos.	Pirquet pos. %	Absentees %
1. Fridalen	1032	69	6.8	1.6
2. Haukeland	430	32	7.5	0.5
3. Solheim	562	47	8.4	0
4. Nygaard	861	74	8.8	1.9
5. Möhlenpris	443	39	9.1	2.9
6. Ny Krohnborg & Gyldenpris	1351	126	9.3	0.3
7. Sandviken	888	86	10.0	1.7
8. Rothaugen	712	72	10.2	1.0
9. Dragefjellet	411	42	10.6	3.1
10. Chr. Krybbe	416	46	11.3	2.2
11. Nordnes	755	87	11.9	3.2
12. Krohnengen	537	69	13.3	2.5
13. Gyldenpris 1—4 classes	(152)	(18)	(12.0)	(1.3)

times the statistical standard error, and comparison is therefore feasible. When the percentage of positive reactors is calculated for each class in these two school groups (fig. 3), confirmation is found of the well-known phenomenon that the age of infection moves up in the least infected communities. The straight lines in the curves for the relative figures represent a flattening-out of the curves according to the method of least squares.

It is difficult to draw a correct picture of the distribution of Pirquet-positive children in the town. Bergen is divided into parishes, and the percentage can be calculated by parish, as in fig. 4—C. This calculation is, however, based on the census of 1939 which is not correct today. Besides, the density of population and the social conditions vary greatly in some respects in one and the same parish, notably the large ninth parish. The percentage can also be calculated by school districts (fig. 4—B.) But this calculation is also not quite correct as the children do not always live in their school districts. However, both charts may together give an approximately correct impression.

The same difficulties present themselves when one seeks to find out the social conditions which influence the percentage of positive reactors. There is great lack of uniformity in the social conditions

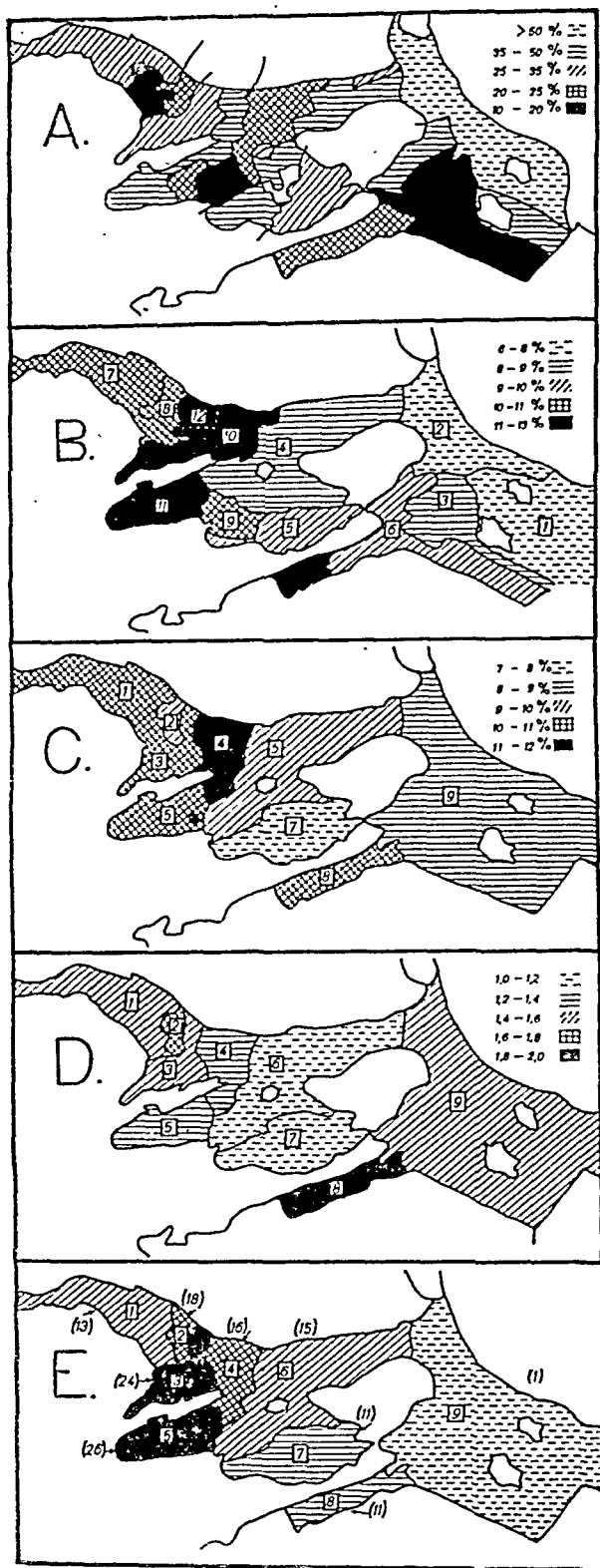


Fig. 4. (A) Chart of Bergen, showing males tested with Pirquet at the age of 19, calculated as a percentage of the males on the military register.

Fig. 4. (B) Chart showing Pirquet-positive scholars in the public schools in the autumn of 1941, calculated as a percentage of the scholars examined by school districts.

Fig. 4. (C) Distribution of Pirquet-positive scholars in the public schools of Bergen in the autumn of 1941. The charts shows the reactors examined between the ages of 7 and 13, and calculated on a percentage basis of these, parish by parish, according to the national census of 1939.

Fig. 4. (D) A comparison of the positive reactors in the national schools with the density of the population classified parish by parish. The number of inhabitants per room from the data of 1937.

Fig. 4. (E) Character of the housing conditions, expressed in figures on the basis of the home's equipment with bath and W. C., its rental and age. These three factors are numbered from 1 to 9, and the figure for each parish (in parentheses) is the sum of these three factors.

in some respects of each parish, and the available statistical data are from 1937. The findings must therefore be considered with reserve. There is little concordance to be found on comparing the percentages of positive reactors in parishes the density of whose population is calculated according to the number of occupants of a room (fig. 4—D). It should be noted that in parishes 5 and 4, the relatively numerous joint households, homes for the aged, boarding-houses etc. give a too favourable impression of the density of population.

There is greater concordance when one compares the percentages of positive reactors with the character of the housing (fig. 4—E). This is expressed in figures on the basis of a home's equipment with bath and W. C., its rental and age. These three factors are numbered from 1 to 9, and the figure for each parish is the sum of these three factors. (The smallest number = the best, and the largest = the worst condition). Only when the morbidity, mortality and opportunities for infection are investigated at the same time, can an opinion be formed as to whether housing conditions and the standard of living influence the risks of infection more than the density of population. Such an investigation would have to depend on more recent statistical data than are at present available.

B. Radiological control.

The further examination of the schoolchildren was by screen-photography of all who were Pirquet-positive, and of all the scholars in the first and last classes of the public schools. Cases, suspect on screening, were kept under subsequent supervision.

Table 5 shows the results of the examination of the Pirquet-positive cases. Active disease of a tuberculous character was found in only 14 of the 113 who were re-examined, i. e. in 12.5 per cent. With growing experience and opportunities for comparing the screen photos from year to year, this percentage will assuredly rise further. This procedure should economize time and render the examination more popular. The many unnecessary summons to examination are upsetting and irritating for those who prove to be well.

Active pulmonary tuberculosis was found in two sputum-negative cases in the public schools and in one sputum-positive case in a

Table 5.

Clinical control of the Pirquet-positive school-children in autumn 1941.

	Public schools	%	Higher schools	%	Total	%
Pirquet positive	854		382		1236	
Of whom were screen X-ray ..	830	97.0	325	85.0	1155	93.0
» » » clin. examined ..	98	12.0	15	5.0	113	9.8
with following findings:						
Active pulm. tuberculosis	2	0.2	1	0.3	3	0.3
» hilus adenitis	10	1.2	0	0	10	0.9
Pleuritis	1		0		1	
Inactive pulm. tuberculosis (under observation)	2		0		2	
Pulm. tbc. invet. (calcif. etc.) ..	21		7		28	
Inactive hilus changes	48		7		55	
Negative lung findings	16		0		16	

higher school. The ten cases of hilus adenitis and the one case of pleurisy were all found in the public schools. The two inactive cases of pulmonary tuberculosis had undergone hospital treatment earlier, and subsequent examination has shown no sign of active disease. The total morbidity among the Pirquet-positive cases undergoing screen-photography was 1.1 per cent.

Among the Pirquet-negative scholars who underwent screen-photography was one with hilus adenitis; Infection had probably occurred in the course of Pirquet testing. Thus the total number of cases of hilus adenitis was 11. A non-specific pulmonary infiltration was found in one case, and heart disease, overlooked at the screen-photography in 1940, in another. As already pointed out by James-Olsen, all the children were photographed on this occasion. In the spring of 1941, all the oldest classes in the public schools were Pirquet tested, and the positive reactors were photographed. Table 6 is a comparison of these two examinations with the last examination. Here are to be found only those cases of tuberculosis which were discovered at the above-mentioned examination, — undertaken at a time chosen at random. These examinations showed a total morbidity of 2.7 per thousand. A comparison of the 1940 with 1941 findings shows that the number of new infections or cases of hilus adenitis is practically unchanged, whereas the

sons. Considering that BCG vaccination figured for the first time on the programme of the Health Service in the spring of 1941 and has always been voluntary, a vaccination percentage of over 45 in the public schools promises well for the future. The small number of vaccinated scholars in the higher schools suggests that advice by word of mouth will be needed to raise the vaccination percentage. A new appeal on behalf of BCG vaccination had been planned for the spring of 1942, but irregularities in the school curriculum made this impossible.

2. *The Environment Examination.*

The second part of the present study concerns the environment examination centring about the Pirquet-positive cases. This examination should be a logical sequel to the Pirquet examination, but it is only of recent years that it has been carried out on any large scale. Such an environment examination must prove fruitful as the infection of the Pirquet-positive must be of recent date, and the possible sources of infection are often limited to the family and the nearest surroundings.

To study more closely the various modes of infection, and in order if possible to detect unknown sources of infection, all the Pirquet-positive cases were charted out on a map of the town. This made it easy to see if several members of the same family are Pirquet-positive, and if in certain houses, quarters or streets there are accumulations of Pirquet-positive cases not traceable to known sources of infection. Such accumulations of Pirquet-positive cases rouse suspicions and call for a closer examination of the environment.

The ideal would be to chart out on the same map all the persons on the tuberculosis register, with a statement concerning their infectiousness. This has not been done. The public health nurses make good this defect to some extent by memory.

The next step was to invite all in contact with scholars in the first class, negative-to-positive reactors and Pirquet-positive members of the same family to undergo examination. There followed the issue of a form of questions to the other scholars with unknown sources of infection, i. e. to about half of all the Pirquet-positive scholars. This form contained questions about known

opportunities for infection, and advice to the other members of the family to let themselves be examined. Those members of the family who turned up were screen-photographed if they were more than 35 years old. Those under this age were Pirquet tested and the positive reactors were screen-photographed.

Fifty-two members of the 99 families summoned turned up. In the next series, a questionnaire, addressed to 560 families, was answered by 264 or 47 per cent. Of the 882 members of the families thus addressed, 453 (51 per cent.) were examined. Of the 854 Pirquet-positive scholars in the public schools, 458 had been examined earlier by the Health Service. In 128 cases (15 per cent. of all who were Pirquet-positive) tuberculosis had existed earlier. The 1236 positive reactors among the children were distributed over 1087 houses. In 139 cases, there was more than one positive reactor in the same house, altogether 303 children or 24.5 per cent. of those who were Pirquet-positive.

The *possible sources of infection* were mainly the following:

1. Parents (in the home).
2. Brothers and sisters. (» » »)
3. Relations (Outside the home).
4. Companions » » »
5. House (In the same house without close companionship).
6. School (Scholars, teachers).
7. Street (Tuberculosis in the same street).
8. Evacuation.
9. Unknown.

These findings and the earlier investigations of the Health Service afford examples of the above-mentioned modes of infection. Parents, brothers and sisters, other relations and companions are such every-day sources of infection that they need no further discussion.

House infection. The system of charting afforded some illustrative examples.

Table 8: On the table, nrs 3 and 4 were positive. Nr 3 had earlier been discovered at an environment investigation centring about nr 1. Nr 4 was a positive reactor in the first class. When the family was summoned for examination, nr 5 proved positive and the sub-

Table 8.

House infection. I.

Family 1: First storey.

Parents: well.

1. Daughter born 1923: miliary tuberculosis in March 1941.
2. Son born 1925: Environment: tub. gld. bronch. in April 1941.
3. Son born 1934: School: neg. to pos. Pirquet reactor. Hilus adenitis in April 1941.

Family 2: Third storey.

Parents: well.

4. Son born 1934: School: Pirquet pos. 1st class in Oct. 1941.
5. Son born 1936: Environment: Hilus adenitis in Feb. 1942; adm. Haukeland Hospital in Dec. 1941, Pirquet pos. and adenit. post angina.

No other children in the house.

Source of infection: man aged 25, lived at home with parents and grown up brother. Consulted doctor for his throat. Found cavernous pulmonary tuberculosis of old standing.

Table 9.

House infection. II.

Family 1:

Parents: well.

1. Son born 1927: Pirquet neg. autumn 1941. Pirquet pos. spring 1942. Well.
2. Daughter born 1932: Pirquet neg. to pos. reactor autumn 1941. Hilus adenitis.

Family 2:

Parents: well.

3. Son born 1917: Pulmonary tuberculosis autumn 1942.
4. Son's daughter 10 months: Pulmon. tuberculosis spring 1942.

Family 3:

Parents: well.

5. Son born 1923: Pirquet pos. 1940.
6. Son born 1931: Pirquet neg. Oct. 1941 and pos. autumn 1942.
7. Daughter born 1933: hilus adenitis 1940.

Family 4:

Parents: well.

8. Son born 1930: Pirquet neg. autumn 1941 and spring 1942. BCG.

No other children in the house, the adults well.

ject of hilus adenitis. This high morbidity made the existence of a source of infection in the house highly probable. This source was

discovered by a private practitioner a couple of days before the investigation of the Health Service was started.

Table 9: On the table, nrs 2, 5, and 7 were positive. This led to all the occupants of the house being examined in the spring of 1942. Nr 1 was then found to be a negative-to-positive reactor. Nr 3 — the source of infection — proved to be a case of long-standing pulmonary tuberculosis. Nr 4 had an extensive lung infiltration. Nr 6 was also a negative-to-positive reactor, only nr 8 was Pirquet-negative and was vaccinated by BCG. It is possible, but not proven, that the source of infection discovered was responsible for the infection of nr 7.

School infection. One example was discovered. In 15 classes, cases of tuberculosis were found on the school medical examination. When, two months later, Pirquet tests were carried out, a negative-to-positive reactor was found in a class in which another scholar suffered from hilus adenitis. All the other scholars proved to be negative with the exception of those in a third, »middleschool» class. In this instance, the school medical examination had revealed the only infectious case of tuberculosis. When the Pirquet testing was repeated, five girls proved to be negative-to-positive reactors. All of them sat near, and notably in front of, the patient. One suffered from hilus adenitis. Another was febrile for a couple of weeks before the examination, and her sedimentation rate was 44 mm — normal radiological findings. A third, the only one to associate with the patient out of school, suffered from hilus adenitis. The two other negative-to-positive reactors were found to be healthy.

The most comprehensive example of school infection dealt with by the Health Service is the following.

In October 1939, a girl, in a class of 30 in the first »middleschool», was notified as suffering from pulmonary tuberculosis. At the same time five other girls were ill, two of them suffering from erythema nodosum. Examination of the class during the five following weeks showed that 25 were Pirquet-positive. Ten suffered from active hilus adenitis, and five showed a high sedimentation rate. Most of the scholars were re-examined in the spring of 1940. One of them, whose sedimentation rate had been raised, had developed hilus adenitis, and one who had suffered from hilus adenitis had developed pleurisy which in the course of a couple

of months turned to destructive pulmonary tuberculosis. One who had been Pirquet-negative was now positive. When the class was screen-photographed in the autumn of 1940, two more cases of pulmonary tuberculosis were discovered. In one of them hilus adenitis had been found in the spring of 1940, whereas in the other nothing had been found amiss at the examination in April. In one case, with a sedimentation rate of 44 mm, an apparently inactive focus, of the size of a pea, was located in the left apex. In the course of a couple of months she developed a rapidly destructive pulmonary tuberculosis, and in February 1941 cavities were demonstrable on both sides. She died in June.

It is possible that this outbreak came to an end in the autumn of 1941 with two deaths, one incurable case, and two undergoing pneumothorax treatment. Only four of the 30 scholars have remained Pirquet-negative, and all of them have been vaccinated with BCG.

It is assuredly no fortuitous coincidence that in both these examples of school infection the scholars were girls aged 14 to 15 years. Ulrici finds this age lacks resistance to infection with tuberculosis is as marked a degree as does earliest infancy. In his opinion, the course of the disease is characteristic, beginning as it does with a simple hilus adenitis which in the course of months and years undergoes destructive changes, without definite pauses, in spite of treatment. Women in particular show this condition, and its mortality is exceeded only by that of miliary tuberculosis.

Street infection. It is difficult to find typical examples as the conditions under which infection occurs are not easily discovered, and other sources of infection may play a part. It is possible that a certain street-infection may serve as an example. In this street, 30 per cent. of the schoolchildren were Pirquet-positive, whereas elsewhere in the parish only some 12 per cent. were so. Two areas indicate the sources of infection. Father and son lived in one area. The father's was an old case of phthisis for which hospital treatment had not been given till 1940. The son suffered from chronic tuberculosis, a drunkard wandering in and out of sanatoriums. In the other area lived a schoolgirl who developed tuberculosis in 1939. Her father was found in the spring of 1942 to be suffering from chronic infectious tuberculosis. About these sources of infection were 17 Pirquet-positive schoolchildren, whose infection could not

always be traced to its origin. Three were scholars belonging to the same class as the girl who developed pulmonary tuberculosis in 1939.

Evacuation infection. A couple of such cases occurred. During the indiscriminate evacuation on the outbreak of war in 1940, tuberculous patients came into contact with healthy persons. Arrangements have since been made for the evacuation of the tuberculous, should this prove necessary, so such disasters should be avoided in the future.

Unknown sources of infection. They continue to be numerous in spite of all. Gastric-lavage examinations have shown that persons without either signs or symptoms of disease may discharge tubercle bacilli sporadically. Primary infections, which often give rise to no symptoms, are also not infrequently associated with the discovery of tubercle bacilli. In the present study it is of little importance that in Norway at the present time these gastric-lavage-positive cases play a subordinate part compared with sputum-positive cases. They can, at any rate, be a source of positive reactions among their surroundings.

To ascertain the frequency of the various modes of infection, the most likely sources of infection have been investigated in the present study in the eight classes of the public schools, class by class. Infection within the family may perhaps be overrated as the data are based primarily on the earlier environment examinations of the Health Service which paid the greatest attention to the family. The environment examinations were more thoroughly investigated in the first three classes than in the remainder, a special summons being addressed to the relations of the scholars in the first class, and the scholars in the second and third classes being Pirquet tested also in the spring of 1941.

In table 10 the number of discovered sources of infection follows the classification adopted in the earlier scheme. School infection is seen to be insignificant. In the group »undiscovered infection» are collected the cases in which no information was obtained from the relations.

It is possible that a more energetic agitation for the environment examination may raise the proportion of known sources of infection for the higher classes to 65—70 per cent. From the third to the eighth class in the present study they are on the average

Table 10.

Probable sources of tuberculous infection for the eight classes of the public schools.

Source of infection	C l a s s								Total
	1	2	3	4	5	6	7	8	
Parents	19	27	23	24	23	34	29	7	186
Brothers & sisters ..	8	5	11	9	8	5	14	3	63
Family	17	17	16	15	16	11	21	10	123
Surroundings	1	4	3	3	10	4	6	2	33
Living quarters	3	7	4	1	3	4	5	1	28
Evacuated	4	1	3	3	1	3	1	0	16
No information ..	11	9	24	23	46	42	44	27	226
Not known	10	5	16	23	23	34	59	9	179
Nr. positives	73	75	100	101	130	137	179	59	854

just over 47 per cent. We observed that home infection remains fairly constant — about 55 per cent. — among the known sources of infection, and that family infection constitutes as much as 83 per cent. of the known infections.

As already mentioned, a study of the conditions under which the infections occurred showed that there were two or more Pirquet-positive persons in each of 139 houses. The 303 scholars concerned may be classed in three groups:

1. Positive brothers and sisters in the same home, 92 houses, 189 scholars.

2. Other positive reactors, different homes, 47 houses, 98 scholars.

3. A combination of 1 and 2 (15) houses, 16 scholars (+ 31).

In the first group, the source of infection was found in 74 per cent. and 70 per cent. of the infection was familial which dominated by 75 per cent. among the known sources of infection.

In the second group there were 47 scholars with known sources of infection, 15 scholars in six houses being infected from the same source.

In the third group there were 47 scholars, 31 of whom belonged to the brother-and-sister group. The source of infection was discovered in 32 cases in nine of which the source of infection was one and the same in three houses.

The environment examination revealed six new sources of

infection, sputum-positive cases in three instances, gastric-lavage-positive cases in three others. These findings may perhaps seem paltry after such an extensive investigation. Why more sources of infection were not discovered may be due to the facts that the tuberculosis work has already been carried out efficiently in Bergen, and that this new investigation was undertaken at a time when the public was dominated by war problems, witness the fact that many of the persons summoned failed to turn up. Only 47 per cent. of the questionnaires were answered, and only 51 per cent. of the members of families mentioned therein appeared for examination. In other words, only one-quarter of the school-child environment in which the sources of infection were unknown was examined.

Discussion.

The present investigation is intended to serve as a basis for a yearly tuberculin examination of the schoolchildren in Bergen. With its 11,000—12,000 schoolchildren, this work should be within the scope of the Health Service. With the help of the school nurse and two persons from the Health Service, the tuberculin examination can be completed in three weeks. The subsequent examination of the tuberculin-positive can be carried out in a short time by screen-photography without the routine work of the diagnosis station being neglected.

The environment investigation about the scholars with positive reactions is the most important part of the tuberculosis examinations. Between 50 and 70 per cent. of all the infections occur at home or in the immediate surroundings. Environment investigations bring schoolchildren and homes in contact with our tuberculosis work, establishing mutual interest for the future.

Environment investigations require no great machinery after the first year. By an arrangement for the screen-photography of persons over 35 years and of the tuberculin-positive under this age, the examination itself can be quickly completed. The annual examinations can be made to include the environment of negative-to-positive reactors and positive reactors in the first class, — some 100 and some 70 respectively. The environment examination of negative-to-positive reactors is obligatory. This should also be

the case for the positive reactors in the first class in which over 80 per cent of the infection assuredly occurs in the immediate surroundings. Once the environment examinations have been completed for the first class and for negative-to-positive reactors, the environment of all positive reactors among the scholars in the public schools will have been examined in the course of seven years.

The effectiveness of the examination could be further enhanced by combining it with a charting of the tuberculin-positive with a view to discovering house or street infection if it exists. Such an examination must prove fruitful considering that tuberculosis in the environment of children is reflected in their positive tuberculin reactions. It should prove a cheap and very effective auxiliary to the other prophylactic measures against tuberculosis, particularly in the most asocial environment in which children are usually numerous.

As already mentioned, this investigation should also prove of value both in determining the time at which infection occurs and in following the changes in the tuberculin reactions and their possible dependency on the environment.

Summary.

In the autumn of 1941, the schoolchildren of Bergen, about 11,000, were Pirquet tested. The environment of the 854 scholars in the national schools, found to be Pirquet-positive, was examined with a view to ascertaining the frequency of the various modes of infection.

1. *The Pirquet Investigation.* The percentage frequency of the positive reactors in the national and in the higher schools was calculated class by class. The rise in this percentage found in the seventh class seemed to continue upwards.

2. The distribution of the Pirquet-positive scholars in the in the national schools of the town was investigated in relation to the density and housing conditions of the population. Definite conclusions could not be drawn because the statistical data were defective.

3. The Pirquet-positive scholars underwent screen-photography, 1155 of 1236 positive reactors being photographed. Three cases

of pulmonary tuberculosis, in one of which tubercle bacilli were found, 11 cases of hilus adenitis and one case of pleuritis were discovered.

4. The environment examination of the Pirquet-positive reactors showed that more than half of those found to be positive were already known to the Health Service. Six new cases of infectious tuberculosis were discovered.

5. The various modes of infection and their frequency were studied, and characteristic examples of house, school, and street infection are mentioned. Lastly, the modes of infection are calculated class by class in the national schools on a percentage basis.

As a result of this investigation, compulsory environment examinations centring about all the tuberculin-positive scholars of the national schools, or, contingently, the positive reactors in the first class, are recommended as an important part of the campaign against tuberculosis. The recording of positive reactors on a chart is helpful in revealing house and street infection. The medical examination for tuberculosis of schoolchildren is of little prophylactic value in the tuberculosis campaign without environment investigations. A highly prophylactic measure against tuberculous disease is BCG-vaccination of all tuberculin-negative persons graduating from the public schools, the vaccination being repeated every time the tuberculin reaction again turns negative.

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On Recovery from Diabetes Mellitus.

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Recovery from diabetes mellitus is a very moot question, and, of course, depends on the definition of the disease. For the purposes of this paper the author's definition of »clinical diabetes mellitus» is the full syndrome comprising the cardinal symptoms of thirst, polyuria, loss of weight and loss of strength, coupled with the chemical findings of hyperglycæmia, glycosuria and ketonuria.

The majority of workers are sceptical about complete recovery from this clinical condition ever occurring, in spite of the positive, if rare, evidence provided by the literature. In the days before blood sugar estimations were developed, some striking cases were published of patients who recovered from what was apparently diabetes mellitus.

The first available reference to such a recovery is a case published by Holsti (15) in 1892 of a man of 41 who had an acute onset of thirst, polyuria and glycosuria after influenza; within a month all the symptoms went and on a full and normal diet he had no glycosuria. The evidence in this case seems clear enough, but it must be admitted that in those days blood sugar estimations were not available, and therefore the diagnosis might be called into question.

In 1901 Achard and Loeper (1) wrote that, whilst there must be every grade of »L'insuffisance glycolytique» between normal

sugar metabolism and frank diabetes, 3 grades can be distinguished: 1. full diabetes mellitus. 2. latent diabetes, which is sometimes permanent but can sometimes be temporarily observed during an acute illness such as »rheumatism», pneumonia, lymphangitis, etc. (This would perhaps be termed by other writers, »mild diabetes» or »toxic glycosuria.») 3. A loss of sugar tolerance only demonstrable by their glucose injection test: this condition again might appear spontaneously, or temporarily during an acute illness such as the above, or during severe cachetic diseases.

The shortest attack of diabetes on record was that of Hürter's (16) (1910) a child of 10 $\frac{1}{2}$ who suddenly developed severe thirst, polyuria, wasting and hunger, with a very heavy glycosuria (9 %) and a positive ferric chloride test on the urine. The whole syndrome lasted only 7 days: on a full normal diet, there was no recurrence of the symptoms or of glycosuria in the 10 months after recovery.

Mann's (26) (1904) case was perhaps less surprising: a man of 45 was under observation for jaundice due to carcinoma of stomach, subsequently at autopsy shown to be invading the pancreas; he had an attack of severe thirst and polyuria with heavy glycosuria, which lasted 2 weeks only and then completely disappeared. This case tallies with the very occasional diabetes which develops after acute pancreatitis.

Wallis & Roper's (36) (1912) case, a man of 19, had an acute onset of thirst and polyuria with glycosuria and acetonuria starting after recovery from »Java fever». On a fixed diet of about 100 grams of carbohydrate a day, the glycosuria and acetonuria were strikingly intermittent for a period of 3 months. The remissions seemed very complete for in one of them there was no glycosuria after a heavy starch meal, in another the patient had an attack of influenza without any glycosuria appearing, even after being given 100 and again 180 grams of glucose by the mouth. The symptoms and glycosuria eventually permanently vanished and did not reappear during subsequent follow-up.

That the severity of diabetes in individual diabetics is variable must have been known since the days of Hippocrates; but since the advent of blood sugar estimations, and insulin treatment, more exact information as to such variability has been obtainable, especially when combined with clinical assessment of the patient's condition, based on better clinical knowledge.

If it be granted that the severity of the diabetic state in patients can be deduced from the amount of insulin daily required to keep them in good health, to keep the urine consistently free of sugar, and the blood sugar within normal limits, then spontaneous improvements in diabetes can be observed in the following ways.

First, after an acute severe case of diabetes is brought under control by diet and a certain dose in insulin, it is often necessary to lower the dose of insulin within a week or two, to reach the maintenance level. Secondly, as the patient's age advances beyond 50 years, quite often the insulin requirement gets slowly less over a period of years. Thirdly, a diabetic patient, who has for a year or two had the same daily insulin requirement may suddenly start having hypoglycæmic attacks; he is then found to need a much smaller dose of insulin, though his diet remain the same. A sudden reduction in insulin requirement of 30 to 50 per cent is not infrequently seen amongst patients in a big diabetic clinic.

Finally, an established diabetes can be made worse by an infection, or an unsuspected diabetes be brought to light by an inflammatory process, such as a carbuncle. In the former case, as the infection clears, the diabetes improves, or put in more modern parlance, the insulin sensitivity increases: in the latter case, the patient may be left with a very mild diabetic condition, which was probably present before the infection, though it gave rise to no symptoms; in some cases the sugar metabolism may even recover completely to normal. In view of these facts, it is not surprising that spontaneous recovery from diabetes can occasionally be encountered, rare though this seems to be.

The object of the first part of this paper is to show evidence that recovery from diabetes mellitus is possible; that the disease can occur temporarily and then completely disappear. To this end, a series of cases will be described, each of whom had one or more attacks of diabetes followed by recovery to normal.

The criteria of recovery from diabetes mellitus are that, on a normal unrestricted diet and without taking insulin, the patients 1. are free from symptoms, 2. have a normal carbohydrate metabolism. The latter is proved by their having (a) no glycosuria, (b) a blood sugar which, whatever the carbohydrate intake may be, at no time of day rises above 180 milligrams per 100 cm³ (c) a normal sugar tolerance, i. é. if after taking 50 grams of glucose when

fasting, their blood sugar does not rise above 180 milligrams per 100 cm³, and in 2 to 3 hours shows the characteristic «overshoot» to below fasting level. Criteria 1, and 2 (a) and (b), are not by themselves absolute proof of recovery; they are compatible with a mildly abnormal sugar metabolism. Criterion 2 (c) cannot occur in the presence of diabetes. If a patient, who has had the usual clinical syndrome of diabetes and has needed insulin for controlling the disease, comes later to fulfil all these criteria, then he or she may be said to have recovered from diabetes mellitus.

The disappearance of the symptoms of diabetes is a separate and distinct matter. It is well known that when a diabetic patient starts treatment, the classical symptoms of the disease tend to be lost long before the sugar metabolism of the patient approaches normal, i. e. before the blood sugar is within normal limits and the urine free of sugar and acetone.

That the symptoms of the disease can vary independently of the disease itself is shown by a second series of cases, which consist of patients who had transient attacks of severe thirst, polyuria, loss of weight and strength; these symptoms came and went although the disturbance of carbohydrate metabolism persisted with little or no fluctuation.

Methods.

Blood sugars were estimated by the standard Maclean's technique; for convenience the abbreviation B. S. x. is used indicating a blood sugar concentration of x milligrams per 100 cm³; unless otherwise stated, the estimation was done between 3 ½ and 4 ½ hours after breakfast. The urine sugar was not estimated, but the following degrees of glycosuria are described. S +++ means a heavy reduction with Fehling's solution and thus indicates a concentration of 2 grams per 100 cm³ or more; S + means a yellow precipitate with Fehling's solution and thus an approximate concentration of 0.5 to 1.0 grams per 100 cm³; the specimen tested was that passed first in the morning on rising. Rothera's test for acetonuria was used, and the abbreviations Ac ++ and Ac + mean an heavy or moderate acetonuria respectively. The diets are shown as Cy, y being the grams of carbohydrate allowed per day. For cases having 2 doses of ordinary insulin, the distribution of carbohydrate at the 4 meals was 1/3, 1/6, 1/6, 1/3 of the total

allowance. For cases on protamine zinc insulin, or no insulin at all, the distribution was $\frac{1}{4}$, $\frac{1}{4}$, $\frac{1}{4}$, $\frac{1}{4}$. No restriction was placed on the protein or fat intake, these being left to the patient's taste and appetite.

Sugar tolerance tests were done as follows. In the morning the patient, who had had no food since the previous evening meal, had a sample taken for fasting blood sugar estimation; he or she was then given 50 grams of glucose in 100 cm³ of water flavoured with lemon; samples of blood were then taken at 30, 60, 90, 120, 150 minutes afterwards. The results are expressed thus: S. T. T. = a: b, c, d, e, f, the letters indicating blood sugar concentrations in milligrams per 100 cm³, a resting, b, c, d, e, f, after the glucose. Cases under observations as out-patients were seen at intervals of not more than three months; they reported at least every month at the beginning of the follow-up period after an acute stage was passed; subsequently they came up at longer intervals.

First series.

Case 1. L. W. aet 29. In the middle of the 8th month of a normal pregnancy, suddenly developed thirst, polyuria, and obvious wasting. A week after these symptoms started she was found to have urine S + + +, Ac + +, B. S. 370. She was put on a diet of C150; with this it was found that at first she needed 100 units of ordinary insulin b. d. to control the diabetes. 2 weeks later the insulin requirements had fallen to 60 units b. d., on which tests showed So, Aco., B. S. 69. On the day following the birth of a normal child the patient had a severe insulin reaction at noon. Only 4 days later she was taken off insulin altogether, and the diet increased to C120. One month later she showed So, Aco, B. S. 117. A S. T. T. gave the following result 85: 100, 133, 109, 109. She was then allowed an unrestricted diet and discharged from hospital. Tests a month later showed So, Aco, B. S. 109. She remained perfectly well for 6 months. She has not attended the clinic for 3 years.

Case 2. S. H. aet 26. His history was that for 2 months he had been abnormally thirsty, and had lost a stone in weight; apart from these symptoms he had been well until 2 weeks before being seen, when he developed an attack of boils. Tests showed S + + Ac? S. T. T. 120: 220, —, —, 190. On a diet C120 and insulin 5 units a. m. and 10 units p. m. he became sugar-free permanently in 3 weeks, and quickly gained weight. 2 months later the boils having cleared, he was taking a full diet and having no insulin. A S. T. T. gave the figures 85: 141, 100, 92, —. Urine showed So, Aco.

Discussion. Cases 1 and 2 were undoubtedly diabetics as defined above, but the error in carbohydrate metabolism was only temporary. In case 2 the diabetes preceded the staphylococcal infection by 2 months. Both patients recovered from the disease, as far as available methods of testing can prove; whether or not they are liable to develop temporary or permanent diabetes in the future is another matter and is impossible to prove, except by watching them for the whole of their lives. Comparable cases are hard to find in the literature. Illman and Wendt (17) (1939) describe a case of moderately severe diabetes in a man of 47, in whom the disease gradually disappeared over a period of 4 years. 11 years later he fulfilled all the criteria for complete recovery. John's (18:1) (1925) case was that of a woman of 37, who initially had severe hyperglycemia but no ketonuria: 4 months after starting treatment, which was by diet only, she had no diabetes by all available tests. Norn's (28) case (1937), a woman of 62 had acute severe diabetes, needing insulin for treatment: over 2 years the insulin dosage was gradually reduced and finally given up. 10 years later she had no sign of diabetes, although the sugar tolerance was slightly reduced. Leyton (24) (1930) describes gradual recovery from severe diabetes in a man of 49: a year later the only abnormality was a 'lag' sugar tolerance test. 2 years later the recovery was maintained, as evidenced by the absence of symptoms, normal urine, and resting blood sugar. Glassberg (12) (1938) reported 6 cases of elderly obese patients who had hyperglycemia and glycosuria; 4 had symptoms of diabetes and 2 had not; all evidence of diabetes disappeared when their weights were reduced, all eventually had normal sugar tolerance tests. Lawrence and McCance (22) (1931) described a case of gangrene of the buttocks and glycosuria in an infant, in which they thought that the gangrene was secondary to diabetes; the infant recovered from the gangrene in a few weeks and all traces of glycosuria disappeared.

Case 3. J. M. aet 47. A policeman, previously perfectly healthy apart from moderate obesity, began to get thirst and polyuria, and lost weight. When first seen, clinical examination showed no sign of infection or other abnormality apart from B. S. 256, urine S + + + Ac + + +. The glycosuria was abolished by diet C100, and insulin 14 units b. d. Over the next 2 years the insulin was gradually reduced and finally given up, the diet being concurrently increased to a full and unrestricted carbohydrate

intake. On this, tests consistently gave So, Aco, B. S. never more than 100, for a further 2 years. Then the previous symptoms of thirst, polyuria and loss of weight returned; after 2 weeks of these the findings were S + + + Ac a trace, B. S. 360. For 2 months he took his original diet of C100 but no insulin. In a further 2 months he gradually returned to a full normal diet again; at the end of this time the urine showed So, Aco, with a B. S. 140. He remained well for a year and then developed a crop of boils. On testing S + + +, Ac + + + B. S. 330 were found. 5 months later, again on a full diet, he would found to have So, Aco, B. S. 170 and for a further year no glycosuria appeared. He then developed a large carbuncle on his neck. With this he went into «precoma»; he was vigorously treated at another hospital and discharged thence on his original diet and insulin 25 units b. d. 5 months later, on an unrestricted diet and no insulin, his urine again contained So, Aco. A S. T. T. done recently, after a further year, showed the figures 117: 211, 113, 109, 104. 3 weeks previously he had had a heavy glycosuria with boils and a carbuncle.

Discussion. This case is extremely interesting and shows 4 attacks of diabetes, with intervals of up to 2 years, during which he was apparently normal. 2 of the attacks were apparently diabetes only, 2 were 'relapses' associated with staphylococcal skin infections. The most recent tests showed but slight loss of sugar tolerance. No similar case has been found in the literature.

Case 4. Mrs. M. T. aet 70. Had suffered for 6 months from severe thirst, polyuria and loss of strength, although her weight was said not to have diminished. When first seen, the patient was almost comatose with urine S + + +, Ac + + + B. S. 500. To rescue her, 500 units of insulin were needed in the next 24 hours. After 10 days on a diet C100 and insulin 40 units b. d. she began to have insulin reactions. The insulin was gradually lowered and finally given up. 7 months later she was taking a full normal diet, was having no insulin, and yet the 24 hour collection of urine was constantly free of sugar. For 3 months she remained perfectly well and then began to lose her appetite, and to suffer from blurred vision. On finding S + + +, Ac + + +, B. S. 420, she was again treated by a diet of C100 and 40 units of insulin b. d. Over 2 months the insulin was gradually given up again, and after a week or two the findings were So, Aco, B. S. 140. Then suddenly, from being apparently quite well, she relapsed into precoma. Owing to the war no further information has been obtainable about her.

Case 5. G. M. aet 36. He was first seen with a 2 weeks' history of thirst, polyuria, loss of weight and failing vision. He had previously always been healthy except for an attack of poor vision a year or two before, which had recovered spontaneously. Findings were S + + +, Ac + + +, B. S. 500. He was given a diet of C100 and insulin 35 units b. d. At the end of a week he was found to have So, Aco, B. S. 30. Only 3 weeks later, while still in hospital, he was found to have, on a full and normal diet taking no insu-

lin, So, Aco. B. S. 80. A S. T. T. then gave the figures 90: —, 200, —, 120, —. For 6 months he remained on a full diet, was perfectly well and had no glucosuria. He then developed polyuria and loss of weight but no abnormal thirst: he also had symptoms and signs of peripheral neuritis in his right leg. Findings were S + + +, Aco, B. S. 380. On a diet C 200 and insulin 40 units b. d. the urine cleared; by the end of 4 weeks though he was no longer taking insulin, he was found to have So, Aco, B. S. 40. In the next 2 months the glycosuria gradually returned; the noon blood sugar rose slowly from 30 to 220. Maintaining the same diet he was put on to protamine zinc insulin, 8 units every morning. For a year he has had a sugar-free urine, except on one occasion; the B. S. has varied from 80 to 300; he has all the time been quite well.

Case 6. T. G. aet 46. Suddenly developed thirst with a certain amount of polyuria; otherwise he remained in his normal health. He reported to hospital 3 weeks from the onset of his symptoms, when he was found to have S + + +, Aco in the urine, and a blood sugar 349. He was given a diet C100 and protamine zinc insulin, 6 units every morning. 6 weeks later all symptoms having disappeared, and the findings being So, Aco, B. S. 100, the insulin was stopped and he was allowed a full diet. A S. T. T. then showed 95: 109, 177, 122, —, glycosuria appearing after the first hour following the glucose ingestion. 5 months from the onset, the findings were So, Aco, B. S. 166: he was in perfect health and had none of his original symptoms.

Case 7. H. S. aet 32. This man came to hospital complaining of thirst, polyuria, loss of weight, and urethritis of a few weeks standing. He was a heavily built man, and on general physical examination he was normal. His urine contained S + + +, Ac trace, B. S. 370. As an in-patient he was treated by diet C120 and insulin 10 units b. d. The glycosuria and all the symptoms cleared up within a week. 3 months later the insulin was discontinued and he was allowed a full diet; at this time the S. T. T. was 97: 166, 171, 117, 100, and at the end of the test the urine showed S trace Aco. He was kept under observation for 5 years and S. T. T.'s have given the following results: —

	<i>S. T. T.</i>	<i>Urine at end of S. T. T.</i>
1st year	109: 216, 191, 141, 113.	S +, Aco.
2nd »	141: 227, 256, 133, 117.	S + + +, Aco.
3rd »	120: 117, 266, 162, 146.	
4th »	95: 133, 206, 109, 104.	S +, Aco.

During all this time he has been on full police duty; he has taken a full normal diet, and has had no insulin; his weight has stayed at 15—16 stone, and he has never confessed to any recurrence of his former symptoms.

Discussion. Cases 4 and 5 had recurrent attacks. It is unfortunate that no further information is forthcoming about case 4.

In case 5, diabetes of a not very severe type eventually persisted. Cases 6 and 7 had single attacks of true diabetes mellitus from which they recovered. It may be argued that the last tests on case 6 show a mild loss of sugar tolerance, and that he therefore comes under the definition (*vide infra*) of a 'reduced tolerance case.' Case 7 also recovered from all symptoms, but he has shown a persistently reduced sugar tolerance.

From the evidence published by Leyton (24) (1930) on a man who recovered from severe diabetes sufficiently to give up insulin, it may be concluded that he was considered, 2 years later, to be a mild diabetic or potentially one. Case 5 was of a similar nature. Mauriac (27) (1934) records the case of a man of 35 who had 3 attacks of diabetes, arising spontaneously; he eventually developed permanent diabetes. Jouve-Balmelle (21) (1935) reports 5 cases who had recurrent attacks of diabetes though the evidence given is insufficient to prove complete recovery in between attacks, and indeed this seems doubtful. In the pre-insulin days, 2 cases of recovery from »absolute diabetes» are recorded. That described by Geyelin and Du Bois (11) (1916) recovered in 4 months to a 'sugar tolerance' of 110 grams per day. Christie's (6) case (1917) had 2 exacerbations in 3 years, both severe enough to bring the patient to the brink of coma; 4 months after the last attack, there were no diabetic symptoms and the patient could tolerate up to 60 grams of carbohydrate per day without glycosuria.

Case 8. J. R. aet 67. Had an attack of boils lasting 2 months during which time he had considerable thirst, polyuria, and loss of weight, also general weakness. In hospital, tests showed S + + +, Ac + + +, B. S. 291. He was therefore put on to a diet of C100 and insulin 12 units b. d. After a week, the findings were So, Aco, B. S. 111. A month later the boils having all cleared, he was taken off insulin treatment. 3 months later he was taking a full diet, and tests showed So, Aco, B. S. 191. For 3 years he has remained well and free from any symptoms, and a recent S. T. T. gave the figures 90: 187, 168, 156, 100, 85.

Discussion. This case had all the symptoms and signs of full clinical diabetes during an attack of boils; 3 years later he has no clinical evidence of diabetes and a sugar tolerance test is normal. It is well known that exacerbations of chronic diabetes are caused by infections, especially of the skin and the upper respiratory tract. Also, symptomless mild diabetes may be found as the result

of a patient coming under observation for some infection; after this clears up the diabetes persists, and was probably present before the infection. There are several published reports of cases of temporary diabetes accompanying an infection. Fykov (10) (1939) describes a child of 2, who developed diabetes, needing insulin for treatment; a lobar pneumonia was found by X-ray examination only. 2 weeks after this had cleared up the child was, by all criteria, free from diabetes. Jonas and Pepper's (19) (1917) case in the pre-insulin days recovered from diabetes accompanying a pulmonary infection; as evidenced by the urine and resting blood sugar tests whilst taking a full normal diet, all traces of diabetes had gone. Ferrabouc et alia (9) (1939) detail a case of a severe diabetes accompanying streptococcal arthritis of the knee; 6 months later by all criteria no diabetes remained. Bowen's (4) case is also interesting; 19 months after the start of a severe diabetes accompanying an acute upper respiratory infection, the patient had by all tests recovered from diabetes. Yet 2 months after showing a normal sugar tolerance test, he died suddenly in diabetic coma; this apparently came on spontaneously, without any known infection.

General Discussion.

Here, then, we have 8 cases showing in all 15 »attacks» of severe diabetes mellitus; only 3 of the attacks were precipitated by a known infection; in all the others thorough clinical examination failed to reveal any inflammatory or endocrine disturbance elsewhere in the body, nor did any evidence of such lesions appear later. Moreover, during the acute attacks, the patients had fully developed diabetes, namely, the full syndrome of thirst, polyuria, loss of weight, and of strength, with hyperglycæmia, glycosuria and acetonuria.

Before passing on to a discussion of the possible varieties of attacks of diabetes, two points must be cleared up. The first is the difficult question of the assessment of the severity of diabetes in any particular case. Are we to measure it by the severity and rate of onset of symptoms, or by the fasting level of the blood sugar before insulin treatment is started, or by the daily dose of insulin required to control the symptoms and maintain the metabolism as nearly

normal for as long as possible in the 24 hours? Or by a more strictly mathematical method such as the insulin sensitivity measured by the tests described by de Wesselow and Griffiths (7) (1938) or by Himsworth (14:1) (1936)? In the present series, no measurements of insulin sensitivity were made. We are dealing with changes in the severity of individual diabetes; if a patient is taking a reasonably constant diet of a moderately high carbohydrate content, the insulin sensitivity can be assumed to be at or near the maximum; therefore discussion is based on the premise that changes in the insulin requirement reflect changes in the severity of the diabetes, that the more insulin a given patient requires, the 'worse' the diabetes, and vice versa.

The second question is, is there such a condition as potential diabetes and is it recognisable? Is there any evidence upon which we can say that a person is likely to develop the full syndrome of diabetes mellitus? We have some information from the familial and hereditary nature of diabetes. In the words of Joslin (20) (1940. 1) «the difference between the incidence of diabetes in the blood relations of diabetics and of the control population is statistically significant». Even more striking is the occurrence of diabetes in identical twins. It may be definitely said that the blood relations of diabetics are themselves potentially diabetic. Further support for the idea is given by Joslin (20) (1940. 2), by Tyner (34) (1933), Sherrill (33) (1921), Pannhorst (29) (1936), and by Lemser (23) (1938), all of whom found a high incidence of abnormal sugar metabolism in the blood relations of diabetics.

There is also the well established connection between obesity and diabetes. Joslin (20) (1940. 3) states that obesity precedes the diabetes in 60 % of cases. Embleton (8) (1938) describes the incidence of sugar tolerance tests tending towards the diabetic type in 35 % of obese females tested, and in 70 % of obese males. Glassberg (12) (1938) amongst many other writers showed recovery to normal sugar tolerance tests in overweight patients who had glycosuria and hyperglycæmia with diabetic symptoms, when their weights were reduced to normal.

The answer to the present question whether recovery from diabetes occurs, obviously depends on the definition of diabetes mellitus.

The author's criteria have been given above, because considerable confusion can arise if such a definition be not made clear. It

is well known that there are many persons, usually elderly, but not always so, who have a heavy glycosuria and hyperglycæmia, but no acetonuria, and no symptoms. Such cases may be found at routine examination, such as for life insurance; in spite of their metabolic error, they are and remain in perfect health. The fact that the symptoms and the disturbance of carbohydrate metabolism can be divorced, forms the subject of the second part of this paper.

There are many varieties of disease in which a minor loss of sugar tolerance is found, (*vide infra*), the patients suffering from which do not develop full clinical diabetes mellitus. Hale White and Payne (13) (1927) only regard as diabetic a sugar tolerance test in which the blood sugar content, fasting, is higher than 0.120 per cent, reaches a higher level than 0.200 after 50 grams of glucose by the mouth, and 2 hours after ingestion is higher than 0.120 per cent. Joslin (20) (1940. 3) gives the name of »potential diabetics» to »those with glycosuria closely related to diet who easily become sugar-free with slight reductions, but whose blood sugar fasting is below 0.130 per cent, and never reaches 0.170 per cent after a meal.» John (18:2) gives no definition of what he calls »prediabetes», in fact the term seems synonymous with »mild» diabetes occurring usually in obese patients, who may or may not also have symptoms. Search of the literature has failed to reveal any reports of so-called »potential diabetics» or »prediabetics» developing full diabetes mellitus. Rony (31) (1937) watched 20 obese »prediabetics» for 1 to 9 years and not one of them developed full diabetes. It is clear that a reduced sugar tolerance, even grossly so, is insufficient evidence to say that a patient is going to develop full diabetes mellitus. To sum up, there are only two conditions under which we can say that patients are »potentially diabetic»; either they are blood relations of known diabetics or are considerably over-weight.

Now, in all human disease there are continual gradations from normal to severe disease; there must be then, every grade possible between normal persons and the rare condition called »absolute diabetes» (see references Geyelin and Du Bois, Christie). For the purpose of the present discussion, a group of cases will be separated as coming between normal persons and fully developed diabetics; the criteria of this group are: (a) that they have none of the classical symptoms of diabetes mellitus, (b) there is evidence of abnor-

mal sugar metabolism in the direction of diabetes, viz, occasional glycosuria, but no ketonuria, and/or a blood sugar concentration that 4 hours after a normal mixed meal exceeds 160 milligrams per 100 cm³ and/or a sugar tolerance test in which the blood sugar rises higher than 180 milligrams per cent and shows no overshoot to below the fasting level up to 2 ½ hours after the ingestion of 50 grams of glucose: the patients of the group will be termed Reduced Sugar Tolerance cases. In 4 patients of the present series this condition was observed 6 times in all, after or between their attacks.

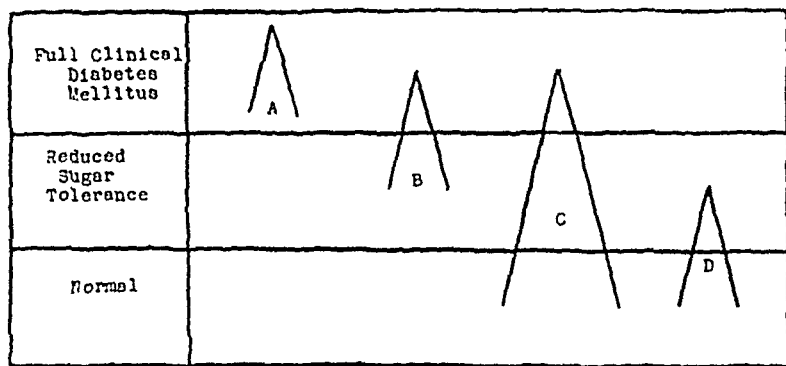


Fig. 1. Varieties of attacks of Diabetes.

If the three groups of cases are expressed diagrammatically as in Figure 1, we can proceed to discuss the possible attacks with subsequent recovery, and see how these are borne out by actual observations.

Attack A. An established diabetic getting temporarily worse and then reverting to the original level. This is a common event amongst patients in a large diabetic clinic; it can happen spontaneously or as the result of an infection. The complete experiment of making a diabetic patient worse by restricting the carbohydrate in the diet to a very low intake and then improving them back to their original level by increasing the carbohydrate in the diet again, has not yet been published; but the second half of the experiment, namely the improvement of diabetes by the taking of a higher carbohydrate diet, is well known; Himswoth (14:2) (1939) in this country and McCullagh and Johnston (25) (1938), in America amongst many other writers have published observations of this kind.

Attack B. A Reduced Sugar Tolerance Case developing full diabetes and returning afterwards to the reduced tolerance level. This sort of attack occurred spontaneously twice in case 5, once in case 7; in the literature Leyton (24) (1930), Mauriac (27) (1934), Jouve Balmelle (21) (1935) report in all nine such attacks. Infection precipitated similar attacks twice in case 3. As a reduced tolerance case would probably be described by the majority of workers as being one of mild diabetes controllable by diet, infection causing a worsening of the diabetes even to the degree of needing insulin therapy is unlikely to cause much surprise, and published reports of such attacks are unlikely to be found. The second half of the attack, namely a case who during a severe infection is found to have full diabetes needing insulin for its control, who when the infection is over is able to discontinue the insulin, is very commonly seen; whether or not the patient before the infection had a reduced sugar tolerance is not known. Again, there is little evidence as to whether a reduced sugar tolerance case can be made fully diabetic by a severe restriction of the dietary carbohydrate; one of the diabetic patients described by Mc Cullagh and Johnston (25) (1938) showed an improvement in sugar tolerance almost to normal on taking a high carbohydrate diet; he relapsed to his original diabetic condition on resuming his previous low carbohydrate intake.

Attack C. A normal person developing full diabetes mellitus and recovering afterwards to normal as far as tests can prove. Such attacks were observed in cases 1, 2, 3, 4, 6 and 8. The attacks were spontaneous in cases 1 (once), 2 (once), 3 (twice), 4 (twice), 6 (once), and also in the cases published by Illman and Wendt (17) (1939), John (18:1) (1925), Norn (28) (1937), Leyton (24) (1930), and Lawrence and McCance (22) (1931). Infection caused the attacks in case 3 (thrice) and in case 8 (once), and similar cases are found in the literature described by Fykov (10) (1939), Jonas and Pepper (19) (1917), Ferrabouc et alia (9) (1939), Bowen (4) (1925). There is no evidence that a low carbohydrate high fat (ketogenic) diet can bring on full diabetes mellitus in a normal person. During the years when severe ketogenic diets were used as the treatment for *B. coli* urinary tract infections, or for epilepsy, no case was ever reported of diabetes being caused by such diets or following the use of them. But there is the well-known connec-

tion between obesity and diabetes, to which reference was made before. 4 out of the 6 cases described by Glassberg (12) (1938) had the full diabetic syndrome; on reduction of their weight to normal, not only did their diabetic symptoms go but their sugar tolerance tests became normal.

Attack D. A normal person having a temporarily reduced sugar tolerance without the symptoms of full diabetes. Such an attack can happen in a variety of ways:— (I) it may be provoked by starvation as first described by Bang (3) (1913) or simply by taking for a period a diet very low in carbohydrate content; this was first observed by Adlersberg and Porges (2) (1926) and has been amply confirmed by many writers. (II) it can accompany various endocrine disturbances such as hyperthyroidism or acromegaly, to disappear if the main disease be cured. (III) it can be produced in dogs by single injections of Young's diabetogenic extract of the pituitary (37) (1936). (IV) it can occur during infections in man or be produced in animals by the injection of bacteria or their toxins. An excellent summary of the literature on the production of reduced sugar tolerance by infections and by bacterial injection is given by Schmidt, Eastland, and Burns (32) (1934). In 18 of their

Table 1.

	Spontaneous	Infection	Low CHO diet	Endocrine	Single Injection anterior pituitary	Obesity
Attack A established diabetes temporarily worse	+	+				
Attack B reduced tolerance case temporarily full diabetes	+	+				
Attack C temporary full diabetes	+	+				+
Attack D Temporary reduced tolerance	+	+	+	+	+	+

Varieties of attacks and the conditions with which they may be associated.

own cases they show that abnormal sugar tolerance tests can be replaced by normal tests when infections had subsided.

Table 1 summarises these various «attacks» of diabetes and the conditions with which they may be associated, and is based upon cases in which good authentic evidence is available. It seems very probable that the gaps may be filled in one day as the result of future observation and experiment. It is also possible that there are many more cases of temporary diabetes than is realised, because the continued good health and satisfactory chemical tests in patients having insulin and/or a controlled carbohydrate diet, may mask the fact that they have really recovered from their disease.

Part 2.

In the preceding section reference was made to the well-known fact that at the start of treatment of a case of diabetes mellitus with insulin the symptoms are usually lost long before the disease is brought under adequate chemical control; that is, although the patient has no symptoms, there may still be hyperglycæmia and glycosuria, and even acetonuria for a considerable part of the day. A passing reference may here be made to a highly controversial paper by Tolstoi and Weber (35) (1940); they report the results of treating diabetes with protamine zinc insulin, regulating the dosage entirely by the patient's symptoms, and ignoring glycosuria and hyperglycæmia. Disappearance of the symptoms then does not prove the complete control of the metabolic disturbance. (But it may be equally well stated, in view of the cases reported in the first part of this paper, that in a few cases who show an apparently perfect symptomatic and metabolic control of their disease, the disease itself may have died out. A patient, who has completely recovered to normal, may easily go on taking a somewhat restricted diet and comparatively small doses of insulin without any untoward symptoms.)

Dissociations of the symptom complex of diabetes from the metabolic disturbance is seen in another way. A large proportion of patients who are called diabetic have hyperglycæmia and glycosuria but none of the classical symptoms of the disease. Such patients are usually, but not always over 50 years of age, and far more commonly women than men. The metabolic disturbance

Table 2.

Type		number	mean of years under observation	percen- tage of all cases	Mortality per cent
under 50 full syndrome	male	191	6.7	55	4.7
	female	159	6.4		6.0
over 50 full syndrome	male	60	5.3	23	6.6
	female	84	5.3		12.5
under 50 symptomless	male	20	7.1	6.0	15
	female	22	6.3		9.5
over 50 symptomless	male	29	4.3	16.0	4.6
	female	73	4.0		10.1
totals		638	5.7		12.7
					8.8

Analysis of cases attending Diabetic Clinic.

may be found on routine urine examination during some minor illness such as a cold or influenza, or furunculosis; it may be discovered at a life insurance or recruits' examination.

Women may come complaining of pruritus thought to be gynæcological in origin. Such cases, especially when no traces of acetoneuria were found were sometimes classified as »benign glycosurias;» for in spite of even gross hyperglycæmia and glycosuria, the patients never had the classical symptom-complex of full diabetes mellitus, and never developed coma. In an analysis of 638 cases under observation in the Diabetic Clinic of St. Thomas's Hospital from 1933 to 1940, 22 per cent were of this type. A brief summary of them is given in Tables 2 and 3.

In a number of them the condition was so mild that they obviously fit into the reduced tolerance group described above. Some of them have had gross glycosuria for more than 7 years, and have had a noon blood sugar concentration of more than 300 milligrams per cent on every occasion on which they were tested; in spite of this they never had any of the classical symptoms of diabetes, never coma, and only occasionally showed a trace of acetoneuria;

Table 3.

	under 50 years old		over 50 years old	
	full syndrome	symptom-less	full syndrome	symptom-less
Unknown	7	2	8	4
Diabetes	5		4	2
Pulmonary tuberculosis	7		1	
<i>Vascular diseases; hypertension</i>			1	
coronary thrombosis			2	
gangrene	1		1	
cerebral hæmorrhage		1		
nephritis				1
<i>Infections; pyelitis</i>		1		
pneumonia			1	2
influenza			1	
pyemia	1			
<i>Other conditions; carcinoma ..</i>			2	1
post-operative pulmonary embolism	1			

Causes of death in all varieties of cases of diabetes in Table 2.

the dissociation between the error in carbohydrate metabolism and symptoms was thus apparently complete.

But some of these cases, besides having the persistent hyperglycæmia and glycosuria, also had attacks of the classical symptoms, which were only temporary. It is with these attacks of symptoms that the second part of this paper is concerned.

Second series.

Case 9. Mrs. W. æt 64. At the age of 59 developed thirst, polyuria, and loss of weight. At that time she was found to have glycosuria but her doctor prescribed no treatment other than medicine. Later she had a carbuncle, during the treatment of which she was put on to a vaguely restricted carbohydrate diet to which she did not bother to adhere; by this time her

original symptoms had completely disappeared. 4 years later she attended hospital for failing vision; apart from this she had no symptoms at all. She was found to have S + + +, Aco, B. S. 340. For the past 2 years she has been taking 20 units of insulin b. d., the diet has been vague. The most recent findings were S + + +, Aco, B. S. 198, and she is feeling quite well.

Case 10. Mrs. W. aet 60. A very obese person who 4 years previously had thirst, polyuria and weakness: these symptoms persisted for 2 years and then disappeared without treatment. For 2 more years she remained symptomless, and then came to hospital for failing vision. This was due to bilateral cataract and retinitis. Tests showed S +, Aco, B. S. 211. For 5 years she has been watched and has kept to a diet (probably) of C 70; she remains perfectly well.

Case 11. S. G. aet 53. He developed severe thirst and polyuria, and lost a stone in weight; these symptoms disappeared without treatment. A month after they had gone he was found to have S + +, Aco, B. S. 330. A low carbohydrate diet was prescribed, but finding that he suffered no ill effects from taking more, he did not adhere strictly to it. For 2 years he remained symptom-free, has been actively at work, and his weight has remained constant. Findings have been S + + + constantly, Ac + + only occasionally, B. S. has varied from 330 to 520.

Case 12. Mrs. N. aet 63. 2 ½ years previously had had an attack of thirst and polyuria lasting a few weeks. She did not feel at all ill nor lose any weight, and the other symptoms disappeared without any treatment. She came to hospital complaining only of weakness. The findings were S + + +, Ac + + +, B. S. 266. For experimental reasons she was prescribed no treatment other than a tonic containing strychnine; the weakness went, as did the glycosuria and ketonuria. 3 months later, still feeling quite well, the findings were S +, Ac +, B. S. 197.

Case 13. Mrs. C. aet 62. At the age of 60, she suffered severe thirst, polyuria and tiredness, and lost 2 stone in weight; she did not consult a doctor, and without any treatment apart from a holiday, the symptoms went and she recovered all her weight and energy. 2 years later she was treated at hospital for a sprained ankle, during which time small subcutaneous hæmorrhages arose spontaneously on two of her toes. She confessed to having felt a little tired and thirsty recently, but not so severely as on the previous occasion. She did not admit to any polyuria or loss of weight. Tests showed S + +, Aco, B. S. 384. On a diet of C70 the symptoms and the glycosuria soon went, and she has remained perfectly well for 20 months and has had glycosuria on one occasion only.

Case 14. Mrs N. aet 60. Originally attended hospital for the symptoms of thirst, polyuria, weakness, and pruritus vulvae. For 2 ½ years she was observed in the diabetic clinic; during all this time, treated by restriction

of diet to C120, she had no symptoms. Tests showed constantly So, Aco and a highest recorded B. S. of 160. The symptoms returned, in spite of continuance of the diet, and she was found to have S + + +, Aco, B. S. 420. Her diet was further restricted to C90: post hoc or propter hoc the glycosuria gradually lessened; 5 months later although the B. S. was 256, urine tests gave So, Aco. 3 years later her diet was considerably freer; she showed So, Aco, B.S. 281, and at the same time was free of symptoms, feeling perfectly well.

Case 15. A. W. aet 52. Had always been quite healthy until he started to get thirst, polyuria, loss of weight and strength. His tests showed S + + +, Aco, B. S. 270. On a diet of C100 and retard insulin 28 units b. d., 2 months later he had So, Aco, B. S. 90. A year later, he was taking a full unrestricted diet and was having no insulin. A S. T. T. then showed 150: 240, 220, 200, 190. Now 4 years later he is still having a full diet without insulin and the most recent findings are So, Aco, B. S. 180.

Case 16. Mrs. L. aet 53. Had an abrupt onset of thirst, polyuria and loss of weight; these symptoms went in 2 weeks, leaving her tired and weak, but otherwise free of symptoms. Tests then showed S + + +, Ac +, B. S. 400. On a diet of C100, to which she but vaguely adheres, and protamine zinc insulin 40 units every morning, the tiredness and weakness have gone. Tests always show So, Aco, though a recent B. S. was 256. Since their first disappearance before treatment, the original symptoms have never returned.

Case 17. A. H. aet 54. At the age of 44 he had developed severe thirst, polyuria and loss of weight; he had been given a very low carbohydrate diet. All the symptoms and the glycosuria went and he was accepted as first class for life insurance 6 months later. 10 years later he was referred to hospital on account of glycosuria. For 3 years under observation, tests have consistently showed S + + +, Aco to + +, with B. S. 162 to 400. His carbohydrate intake has been variable, in the main unrestricted, apart from taking actual added sugar; he remains perfectly well and active.

Discussion. The symptoms always disappear when diabetes is adequately treated. Partial recovery from an initially severe diabetes is common, as seen by the drop in insulin requirements, or increase in insulin sensitivity, soon after a previously untreated diabetic is brought under control by insulin; but the literature contains no reference to disappearance of the symptoms of the disease in patients who have received no treatment and whose carbohydrate intolerance persists. The only case reported in the literature comparable on clinical findings with those herein described, is by Rohdenburg (30) (1922).

A Jewess aged 30, who had a family history of »diabetes«, was found at a routine Life Insurance examination to have glycosuria. Some years later, while on a restricted carbohydrate diet for this, she developed thirst and polyuria, and gradually lost weight. At 40 she had a stormy menopause. From 42 to 45 she never showed glycosuria, even on a full diet. During this time she developed a condition which from the clinical description was clearly myxœdema. Post-mortem examination showed chronic nephritis, cystic degeneration of the adrenals, chronic thyroiditis, and fibrosis of the pancreas with hypertrophy of the islets of Langerhans.

Cases 9, 10, and 11 had hyperglycæmia and glycosuria without acetonuria when they first came under observation for cataract or retinal degeneration; all three gave clear-cut histories of an attack of the classical symptoms of diabetes, namely thirst, polyuria, loss of weight and strength, from which they had recovered without treatment. Case 12 had two attacks of symptoms; the first came on 2 ½ years prior to attending hospital; in the second attack she was under observation; the symptoms again went, as they had done on the previous occasion, without any treatment of her carbohydrate in tolerance. Case 13 also had two attacks; the symptoms in the first attack subsided spontaneously; in the second attack she was treated by diet only. In view of her spontaneous recovery from the first and more severe attack, it is doubtful whether the treatment was the reason for her recovery from the second and milder one. The same doubt exists in case 14, who had two attacks whilst under observation; she was treated by diet for the first, recovered, then relapsed, in spite of continuing her treatment, and then recovered again following only a slight further restriction in her carbohydrate intake; although her diet was again increased after her second attack, she still has no symptoms. Case 15 was considered at first to need insulin, though at no time did he have acetonuria. The insulin was gradually given up when the symptoms had all gone and a mild loss of sugar tolerance persisted, 'controllable' by diet alone. In case 16, most of the symptoms had disappeared before the patient came under treatment. Case 17 was remarkable in that 6 months after a severe attack of symptoms, he was living a normal life and eating a normal diet, and was accepted as a first class life by an Insurance Company. Now, 11 years later he has a moderately severe hyperglycæmia, glycosuria and acetonuria; he has,

however, no symptoms and is for practical purposes receiving no treatment.

It is noteworthy that, with one exception, these patients were all over 50 years of age when they first developed symptoms; also in 7 out of 9 there was no acetonuria at any time. In 2 cases however, acetonuria was found both during the attacks and after. It might be said that these patients had acquired a tolerance to «mild diabetes», and only suffered from symptoms of their metabolic condition got worse beyond a certain critical level. From the evidence, this may have been true in cases 13, 14 and 16; it is less likely in cases 12 and 15, unknown in cases 9 and 10, and in view of subsequent progress and tests, extremely unlikely in cases 11 and 17. It must be here stated that it is not the author's intention to advocate that diabetes over the age of 50 should not be treated. By showing what can be the natural history of the disease, these cases serve to emphasize the difficulty in assessing the results of treatment.

General discussion.

Agreement is not yet generally reached as to the true functional or structural pathological changes underlying the full diabetes mellitus syndrome. If hydropic degeneration of the islets of Langerhans is the structural change, then their regeneration must be the structural basis of recovery. Boyd and Robinson (5) (1925) published evidence of such regeneration. Whatever the process may be, there is no doubt from the evidence here presented, that long lasting recovery from fully fledged diabetes mellitus can occur. How permanent this recovery may be is a matter for speculation. Even if the ultimate cause of diabetes is unknown, it is generally thought that the classical symptoms of thirst, polyuria, loss of weight and strength are easily explicable on the chemical abnormalities. In elderly patients hyperglycæmia and glycosuria may not be accompanied by any symptoms; in a few such cases there may even be some ketonuria. Further evidence of the dissociability of the symptoms of diabetes from the metabolic derangement is afforded by the fact that elderly patients with carbohydrate intolerance can have attacks of the classical symptoms of diabetes mellitus which can pass off whilst the abnormal sugar metabolism persists.

Summary.

1. Details are given of eight cases of severe diabetes mellitus in whom recovery from the disease was observed.

2. The literature on the subject of recovery from diabetes mellitus is reviewed.

3. Nine cases are described of elderly patients with persistent symptomless hyperglycæmia and glycosuria (i. e. »benign glycosuria» or »senile diabetes») in whom the classical symptoms of severe diabetes mellitus came and went without apparent change in the patients' carbohydrate intolerance.

4. The dissociation of the symptom complex from the metabolic disturbance of full clinical diabetes mellitus is discussed.

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Function of the spleen and blood.

By

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Much work has been done about the function of the spleen, and hitherto our really positive knowledge has remained still incomplete. The number of diseases in which this organ has increased in size is large, and of a very divergent nature. This enlargement is easily found and recognized at the examination of our patients, but practically we do not proceed farther than simply ascertaining this fact. If also conditions occur, where the spleen has become smaller, about this clinical indications are missing. If we find an enlargement of the spleen, then it is for us an indication that something in the organism, also outside the spleen itself is out of order and makes it possible for us to come at a diagnosis in combination with other symptoms.

In a great number of blood-diseases the spleen joins to a more or less extent; at least the enlargement of that organ points to a change. That it plays a part in the breaking off of the blood, is generally assumed on good grounds indeed. Likewise many agree that it plays a part as a depot-organ, either as accessory to the blood-distribution in the body or as a depot for special substances, playing a part in bloodbuilding, and of which iron has already been studied most accurately. If this also concerns other building-material, is virtually not known, though there are a few indications that the spleen also plays a similar part for the lipoids of the blood-corpuscles. Also again and again the opinion turns up that it should affect the bloodpreparing organs, viz. the bone-marrow. It should regulate the transition of the completed bloodcorpuscles from the

bone-marrow into the bloodchannel itself, or according to others the spleen has a stimulating effect on the bloodformation.

But on the other hand we know that it is not indispensable, and that the human organism can apparently also live on undisturbed without a spleen. After the removal of the spleen we only see a few typical changes in the morphology of the peripheral blood, be it then that these changes as such are only of a temporary nature. We find normoblasts and other indications that young, not yet matured red bloodcells proceed from the bone-marrow into the bloodstream.

At a few examinations on the territory of experimental anaemias, performed with a view to other symptoms we were at the same time in a position to make some observations about the conduct of the spleen. Because we were working with rabbits, it is not permitted to declare, that which was observed there, is valid for human pathology. We were able to control the conduct of the spleen with two series of anaemic animals. In one group the anaemia had been brought about by the injection of a substance which destroys the red bloodcells. We worked mostly with hydroxylamine. So it is a type of haemolytic anaemia. In the second group anaemia was roused by the drawing off of blood. In both groups we can make a subdivision concerning the intensity and the duration of our experiments. In a part of the animals the anaemic state was only called forth temporarily in connection with further research, and after that was waited till the normal proportions had been attained again, and they were left also for a shorter or longer time on the full bloodvalues. In the other group the anaemia for a longer time was kept on a level as constant as possible. Therewith we endeavoured neither to make the number of red bloodcells drop below the 2,000,000, nor to make it rise above the 3,000,000. The quantity of blood which was drawn off, and the quantity of hydroxylamine which was injected, was always chosen in such a way that this state was kept as constant as possible.

In connection with the other observations the period of time during which our experimental animals were kept on this grade of anaemia, varied from 1 $\frac{1}{2}$ to 14 months. Partly this time was also influenced by the fact that several rabbits could not be kept anaemic for such a long time and that they died under the influence of intercurrent infections. Yet it is remarkable how well the greater

part of the experimental animals behaves during this long period of fairly severe anaemia. At the same time care was taken that they got abundant and varied food, and green fodder was always supplied too in a proper quantity, but never exclusively. Namely, if rabbits are given exclusively green fodder, then in many a slight degree of anaemia appears; if, however, at the same time some bread, oats and carrots are given, then the condition of the blood is best. Also animals made anaemic recover on exclusively green fodder more slowly and less completely than on mixed food. Also when anaemic animals are allowed to choose their fodder themselves, they prefe instinctively mixed food. Of these rabbits the various organs were controlled both concerning their size and composition. It is premised that this examination had not especially been esta-

Rabbit	Weight spleen in mg	Hemo- lysis	Blood- tapping	Further particulars
1	12600	H		was anaemised intermittently during 3 months
2	8100	H		" " " " 8 "
3	7500	H		" " " " 11 "
4	6000	H		" " " " 4 ½ "
5	6000	H		" " " " 6 weeks
6	3525	H		" " " " 7 "
7	2750		B	" " " " 4 months
8	2250		B	" " " " 3 "
9	2000	H		" " " " 10 weeks
10	1100		B	" " constantly " 5 months
11	1000		B	" " " " 6 "
12	950		B	" " intermittently " 10 "
13	900	H		" " " " 9 "
14	900	H		" " constantly " 7 "
15	800	H		" " " " 8 "
16	750		B	" " intermittently " 14 "
17	750	H		" " " " 12 "
18	500	H		" " constantly " 10 "
19	400		B	" " " " 6 "
20	300	H		" " " " 14 "
21	120		B	" " " " 9 "
22	105		B	" " " " 12 "
23	75		B	" " " " 10 "
24	65		B	" " " " 14 "
25	50		B	" " " " 14 "

blished for a study of the function of the spleen, but for that of the fat- and porphyrinemetabolism. The conduct of the spleen was so surprising to us that more accurate attention was paid to that. The normal weight of the spleen of a rabbit amounts to about 1 $\frac{1}{2}$ to 2 grs. Now we have in the following table brought together the weights of the spleen of 25 rabbits, after shorter or longer experiments had been made with them. Behind it is mentioned to what form of treatment they had been subjected during life. We have placed them in order of succession according to the weight, the heaviest spleens at the top.

If we take now the 5 heaviest, then they are all the spleens of rabbits treated with haemolytica. The 5 lightest, on the contrary, belong to the tapped rabbits. This in itself is nothing particular, and might be accepted as a matter of course. What surprises, is, however, the extremely low weight of the 5 last. The spleen was so small that at the obduction we could not find any spleen at first. With difficulty this extremely small organ was found at last. With later obductions we had been prepared for the possibility of such small spleen. All the 5 rabbits belong to the group of the animals anaemised by tapping, in which moreover the tapping-process had been continued without interruption during a lapse of time of more than 9 months. On the contrary we found the 5 heaviest spleens with animals who had been treated a long time indeed but intermittently with haemolytic matter. The normal weights are specially found with animals which had been treated at intervals with tapping or with whom the treatment had been continued a longer time without interruption.

We will exclusively go somewhat further into this so striking atrophy of the spleen of animals with a protracted serious loss of blood, and trace if this may be connected with the existing conceptions about the functions adjudged to the spleen.

In the animal more than in mankind the spleen is the depotorgan for the blood. From here quickly a larger quantity of red bloodcorpuscles can be placed at one's disposal. In a condition of rest the spleen is often four times bigger than in strenuous labour, when all available oxygen-bearers are necessary for the work. With the animal made anaemic with regular blood-topping, all red bloodcorpuscles are continuously in action, and there are too few as a rule, also for the state of rest to be stored in the depots as reserves.

So this function is diminished with our tapped rabbits. Such is also the case with the rabbits treated with haemolytic substances, but we consider the increase in size as the consequence of the part which the spleen plays in the abnormal and constant breaking off of the blood.

With the tapped rabbits a regular breaking off will also occur still, but of course in a slighter measure than normally. But these spleens are so atrophic that it can scarcely be imagined that any breaking off still takes place here. One can wonder if the breaking off now takes place in the bonemarrow which will mobilise all available building-material directly to make head against the constantly high demands for building-up which are put to them. The spleen is also depotorgan for iron. In the spleens of the rabbits which have been treated with haemolytic stuffs, much iron is found. With the tapped rabbits regularly iron is removed from the body; all the available iron must be used directly again; its function as an iron-depotorgan has become superfluous for a long time. The same may be said with respect to the depotfunction of the spleen for the lipoids which must be present continuously for the structure of the new bloodcells, as the iron for haemoglobin. The various depotfunctions of the spleen known to us have become superfluous, perhaps the atrophy is caused by this. Of the other functions described in the course of time there are two which were to occupy themselves directly with bloodformation. The first defended by some writers is the standpoint that the spleen should exercise a stimulating influence on the bloodformation in the bonemarrow. A second conception presumes that the spleen should exercise a checking influence on the outgoings of the erythrocytes from their places of formation in the running blood. The spleen would check a too early going out, and prevent the bonemarrow from functioning too actively. The first conception is hard to bring into accord with the almost entire disappearance of the spleen. For it is the very bonemarrow which must be whipped up to maximal activity, and consequently an extra function of the spleen might be expected. On the other hand it is logical that with tap-anaemia the checking function will fall out. Here all bloodcells made, must be brought as quickly as possible into the blood-channel. When indeed the spleen exercises a checking influence on the bonemarrow also this function will have to be abolished permanently. When we consider

the morphologic blood-picture of these rabbits, then we see that whenever blood is tapped, numerous normoblasts and enormous quantities of reticulocytes find themselves in the blood-channel. We also see with our tapped rabbits that the protoporphyrinegrade of the red bloodcorpuscles has likewise been continuously raised. The protoporphyrine must be considered here as a pre-stage in the development of haemoglobin. The red bloodcorpuscles enter already into the circulation before the haemoglobin has developed itself completely; only in the peripheral circulation the iron is taken up then into the protoporphyrine, and the haemoglobin is brought about. The experiences with mankind agree partly herewith. Directly after the spleen has been taken away, large quantities of normoblasts and reticulocytes enter into the peripheral circulation while also the protoporphyrine of the red bloodcells increases. After a few weeks this symptom disappears again spontaneously, the checking function has been taken over by other organs or tissues. The same is also observed after spleenextirpation in the animal-experiment. After a spleenextirpation also directly a leucocytosis is seen to appear of from 20 to 50,000. The increase of the white bloodcells is therewith fully put to the account of the granulocytes descending from the bonemarrow; the total number of lymphocytes experiences no change therewith.

In this connection the symptoms of congenital icterus should be marked. Herewith the spleen is always enlarged, and it swells still more during the attack. There is increased breaking off of the blood, and this might explain the enlargement of the spleen. But at the same time we see that the bonemarrow is replete with normoblasts and erythroblasts, but these are not transferred to the blood-channel. It has been said that herewith this transition into the blood-channel was checked. Here, too, this function has been bound up with the spleen.

These observations plead very clearly for the checking and presumably regulating function proceeding from the spleen with respect to the transition from the bloodcells of the bonemarrow into the peritheral circulation. The stimulating influence which has been ascribed to this organ, will presumably be more connected with its depotfunction for the various elements, necessary for the building up, such as the iron and the lipoids.

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On the Determination of Urinary 17-ketosteroids and its Clinical Significance.

By

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(Submitted for publication July 26, 1943).

The methods nowadays employed for quantitative analysis of the hormones secreted into the blood are, as yet, far from perfect. Still, a number of methods exist for analysis of the substances excreted with the urine. These substances are identical or closely related with the gland hormones. The methods have been carried out in the hope that the activity of the endocrine organ would be reflected in the amount of these substances in the urine. Particular attention has been devoted to the study of the derivatives of the sex hormones in the urine.

Below, repeated use will be made of the term »hormone analysis». According to the present author, it signifies the analysis of substances with an androgenic activity in the urine. However, the question is, whether »hormone analysis» is an adequate expression, and, further, whether we are justified in regarding substances with an androgenic activity in the urine and sex hormones as equal to one another. The definition of a hormone also covers its occurrence in the organism. Thus, when sex hormones in the urine are mentioned below, reference is being made to *substances with the activity of sex hormones*.

The fact whether the analysis of substances with a hormone effect in the urine offers a standard for the functioning condition of the endocrine gland concerned must still be regarded as an open

question. Clinical experiences have proved that such a connection may actually occur. Castration involves a reduction of the secretion of the sex hormone. A similar condition takes place in the older ages, parallel to the senile atrophy of the gonades. Even other forms of a hypofunction condition in, for instance, the gonades and the adrenal cortex disclose a reduction of the hormone content of the urine. From the urinary content of, e. g., sugar or calcium it is possible to form a conception of the condition of the organism in some particular respect. Thus, our conclusion is based on the fact that our knowledge of the factors in the organism, which regulate the secretion of these substances, is fairly good. Whereas little is known of the factors regulating the activity of the sex hormones in the organism, their destruction, and excretion with the urine.

In the following, the author will give an account of a method for quantitative analysis of substances, with a masculinizing or androgenic activity occurring in the urine. In accordance with a suggestion presented by E. H. Hansen (26), these substances will be comprised in the term «andrin». Thus, substances exerting a specific effect on the morphology of the masculine accidental sex characteristics are denoted by this expression.

Firstly, mention will be made, in brief, of the physiology of these substances.

Up till now, it has been possible to isolate four andrins in the urine, 1. androsterone (in the following denoted with an A), 2. trans-dehydro-androsterone (B), 3. etiocholan — 3 (α) ol — 17 -- on (C), and 4. pregnanediol — 3 (α), 20 (α). (D). The three firstmentioned ones were isolated in the urine of women [Callow, Callow (7)], all four being isolated in the urine from men [Engel et al (17)].

Attempts have been made to find out from which organs these andrins originate. Many facts speak in favour of their development also outside the gonades. Substance B (see above) was ascertained in the urine from healthy [Callow (5); Callow et al (7).] and, also, castrated women [Hirschmann (28)], broadly speaking, in the same quantities as in the urine of healthy men [Callow (6)]. It was found in an increased amount in the urine from a eunuch [Callow, Callow (8)], and from women with virilizing tumours in the adrenal cortex. [Crooke, Callow (11)]. Thus, substance B is formed, during normal conditions, at least, in part, in the adrenal cortex.

The substances A and C have both been ascertained in the urine from healthy and castrated men and women [Callow (6); Callow et al. (7), Hirschmann (28)]. Castrated men, however, excrete smaller amounts than healthy ones. Women with virilizing changes in the adrenal cortex excrete increased amounts of C [Butler, Marrian (4, 35)]. Callow (6) and also Dorfman et al. (15) were able to produce, by means of injection of large doses of testosterone in men, an increased excretion of A and C. From the above-mentioned reasons, A and C should, in all likelihood, be regarded as of partly gonadal and, partly, extragonadal origin.

Substance D has been ascertained in the urine of healthy, pregnant, and non-pregnant women, and of men [Engel et al. (17)].

The adrenal cortex, nowadays, stands to the fore in the discussion of the origin of the andrins. Moreover, it has, in fact, been possible to isolate substances with an androgenic activity from the adrenal cortex, viz., an unsaturated triketone, adrenosterone [Reichstein (42)], and also, a ketocompound with a somewhat stronger androgenic activity [Reichstein, von Kuw (43)]. Thus, the occurrence of substances in the adrenal cortex has been ascertained which, formerly, were considered to be specific to the testis and, accordingly, were called »male hormones». These discoveries are important with regard to an attempt to explain the part played by the adrenal cortex in the forming of the secondary sex characteristics during normal conditions, as well as, principally, in certain morbid conditions. This problem will be dealt with again later.

For a long time, we were restricted to biological determination methods for the analysis of andrins, using, in particular, the cock'scomb test. Pezard (41) was the first to find a direct connection between the growth of the cock'scomb and the added amount of testis hormones. A series of modifications of this method have since been made (see Bomskov's »Methodik der Hormonforschung»). However, the cock'scomb test is affected with many sources of error, principally, those inherent in biological analysing methods in general.

Some of these have been eliminated through the introduction of the international unity (1 I. U. corresponds to the effect of 0.1 mg pure crystalline androsterone), instead of the former exceedingly variable comb unity (C. U.). The results of the analysis vary according to the manner of application of the hormone solution, the

soluble matter, the greatly individual sensitivity of reaction of the test animals, etc.

Other biological determination methods have not been made use of to any great extent (see Bomskov). The biological determination methods have one thing in common, viz., they give a value of the total biological activity in the extract submitted to examination. However, in the urine andrins occur with a lower biological activity, these substances, consequently, being at a disadvantage in the biological analysis.

A chemical determination method with regard to andrins, which has eliminated the above-mentioned obstacles, was first described by Zimmermann (45, 46). It is based on the colour reaction which takes place between 17 -- ketones and m-dinitrobenzene in the presence of alkali. The colour reaction is proportional to the concentration of 17-ketones. However, it is affected by a number of variables, the most important ones being the time of reaction, the temperature, the concentration of alkali, and m-dinitrobenzene and, also, the light.

Callow (9) et al. have tested the reliability of the reaction in detail with regard to andrin analysis. Two conditions are necessary in order that the strength of the colour reaction shall indicate the standard of the andrin content in the urine, viz., firstly, the andrins in the urine must be 17-ketones, and, secondly, the 17-ketones, which occur in the urinary extract, must belong to the substances in the andrin series. According to investigations by the above-mentioned authors, these conditions have been fulfilled. The chemical fractionizing of the urinary extract (see below) concentrates the chromogenous, active substances to the ketone fraction. These substances give, together with m-dinitrobenzene and alkali, an absorption spectrum which corresponds to that of pure 17-ketones. Callow (9) et al. therefore, believe that this determination method denotes a real standard for 17-ketones in the urine. Furthermore, their investigations show that 17-ketones, occurring in the urinary extract, belong to the andrin series.

On the other hand, there are reasons to assume that all these substances do not exert an equally strong androgenic activity at a biological test. Callow (9) et al. and later Friedgood and Whidden (20), and Furuhjelm (21) have, notwithstanding, been able to establish a very good correlation between the results of the

chemical and biological assay. These authors obtained considerably higher values by means of the colorimetric determination method. Friedgood and Whidden (20) are of the opinion that this is due to the presence in the extract of biologically less active andrins which are, chemically, closely related to androsterone and react in the same way as this substance. However, the latter apparently, does not disturb the proportionality between the results of the two determination methods. Accordingly, Callow (9) considers himself justified in assuming that the urinary contents of 17-ketones are also proportional to the contents of biologically active substances. However, the chemical determination method is greatly superior to the biological one, since it gives the total amount of ketosteroids in the urine, even the biologically less active ones. Therefore, this method may, in all likelihood, be ascribed a considerably greater value as an indicator of the andrin metabolism in the organism [see also Gustavson, d'Amour (22)] than the biological method.

The andrins, as well as the estrins, occur in the urine, partly in a free form which is soluble in lipid solvents, partly in a fixed form — probably with glycuron acid — of a non-lipoid-soluble fraction. By means of hydrolysis with a strong acid the esters are transferred to the lipid-soluble form. Then, the andrins and estrins in the urine are extracted with benzol and the benzol extract is treated with alkali (see below), which absorbs the estrins occurring in the extract, thus, causing the andrin fraction to remain in the benzol.

A. *Extraction method.*

4 vol. % concentrated hydrochloric acid are added to an amount of urine, corresponding to 48 hrs. Then, hydrolysis is performed by boiling by means of a reflux refrigerator for $\frac{1}{2}$ —1 hour. The extraction takes place during 12 hrs., with benzol, in an apparatus for continuous extraction.

The benzol extract contains andrins and estrins. These substances are separated acc. to the following procedure. The benzol solution (appr. 500 ml) is shaken twice with 75 ml-portions of a saturated sodium bicarbonate solution (binds acids in the benzol solution) and twice with 50 ml 2-normal sodium hydroxide (binds phenols). The benzol solution is carefully washed twice with 50 ml distilled water and, then, sucked dry. The extract is dissolved in small portions of narcotic ether and filtered through a porcelain filter. The ether is evaporated, and the extract is, then, ready for analysis.

B. Photometric determination.

Reagents: a) *Alcohol.* Ordinary commercial absolute alcohol is sufficiently pure to be used in this connection. b) *M-dinitrobenzene* (extra pure B. D. H., M. P. 89.0° — 89.5°). The reagent is further purified as follows (acc. Callow). 10 mg of dinitrobenzene are dissolved in 375 ml 95 % alcohol, warmed to 40° , and 50 ml 2 N sodium hydroxide is added. After 5 min. the solution is cooled and 1250 ml water is added. The dinitrobenzene settles and is collected in a Büchner funnel. The precipitate is carefully washed with water and recrystallized twice, after an addition of 120 and 80 ml, respectively, of absolute alcohol. Then, well crystallized, colourless needles with a melting-point of 90.5° — 91.0° are obtained.

In the analysis, a solution of 1 gm m-dinitrobenzene in 100 ml absolute alcohol is used. The solution is kept in a refrigerator in a brown bottle. It should not be used if it is more than one week old.

c) *Potassium hydroxide:* 3 N KOH with variations in the titre between 0.999 and 1.002. It is kept in a refrigerator in a brown bottle. No turbidity or colour is permitted.

Determination method: The definitive urinary extract is dissolved in absolute alcohol (Appr. 1/40 of the total urinary vol. Then, this is dissolved with absolute alcohol to a suitable concentration). The alcohol solution has a rather strong colour of its own. Therefore, the solution is shaken with a knife's point of *carbo animalis*, enough to make its own colour disappear. 5 ml of the alcohol solution is mixed in a 10 ml graduated bottle with a ground stopper with 2.5 ml of dinitrobenzene solution and 2.5 ml potassium hydroxide. The retraction of the mixture is compensated with 75 % alcohol up to the 10 ml line. It is well shaken and allowed to stand in a water-bath with constant temp. (20° — 23°) for 60 min. A control test is prepared from the reagent contained in the reaction in the same proportions as in the hormone solution (10 ml absolute alcohol, 5 ml dinitrobenzene, 5 ml KOH, 75 % alcohol up to the 20 ml line). The control test is allowed to stay in the heating-bath for 60 min.

A Pulfrich photometer is employed for the determination. Absolute alcohol in a 10 mm cuvette, and the control test in a 20 mm cuvette, is placed in front of each light window. The adjustment of the photometer is controlled. One of the control tests is exchanged for a test in which the colour intensity is to be determined. Also, the alcohol in the 10 mm cuvette of the opposite side is exchanged for the decolorized alcohol solution of the extract, for compensation of possible remains of its own colour. The light absorption is registered in the spectral filter S 53.

The extinction coefficient (C) is calculated. The noted value of extinction is divided by 2, when a 20 mm cuvette is used.

By means of a standard curve, the andrin contents in the urine are calculated from the value of C. The standard curve is formed on the basis of determinations of the extinction coefficient of pure androsterone solutions of different concentrations. The weight of pure androsterone in 5 ml alcohol (in the graduated retort) is denoted on the abscissa, while the extinction

coefficient is marked on the ordinate. Thus, from the curve the amount of androsterone in the graduated retort may be registered.

Example: 1600 ml urine, corresponding to 48 hrs. The extract is dissolved in 400 ml alcohol (in order to save alcohol, the extract is first dissolved in $\frac{1600}{40} = 40$ ml. Then, 5 ml of this solution is diluted with 45 ml alcohol). The extinction coefficient C corresponds to A mg androsterone in the curve (in 5 ml alcohol). The whole of the alcohol solution (400 ml), or the whole of the urinary quantity, contains $\frac{A}{5} \times 400$ mg 17-ketones or half this value per 24 hrs.

C. Discussion of the method.

1. The hydrolysis has been a subject of discussion. Different observers employ varying amounts of hydrochloric acid and varying times for hydrolysis. The present author has made use of the directions given by Callow (9) and Furuhjelm (21). The urine is acidified to pH 1 with 2 vol.-% concentrated hydrochloric acid. Hydrochloric acid is added in a surplus amount, viz., 4 vol.-%, in order to ensure the attainment of pH. Acc. to Callow, complete hydrolysis takes place by means of boiling with hydrochloric acid for 1 hour. The extraction is complete after 12 hrs.

2. The separation has been performed according to Callow and Furuhjelm. The mode of procedure varies considerably with different observers. For this reason, the present author has tested the reliability of the above-mentioned method by investigating whether the benzol solution contains any estrin, in addition to the andrin fraction, after the separation.

In three cases, the benzol solution was sucked dry and the extract was dissolved in 6 ml oil. In each case, 10 castrated female mice were injected with 3×0.1 ml of the oil solution. Vaginal scraping was performed and examined in the usual manner. None of the extracts, subjected to examination, disclosed any estrus in the animals.

The present author has also investigated to what degree a further treatment of the extract with alkali would affect the andrin analysis.

The benzol solution was divided into two parts. Part A was separated according to the above-mentioned scheme. Fraction B was first shaken with 2×75 ml bicarbonate solution and, then, with 6×25 ml sodium hydroxide. The result will be seen in the table below.

Table 1.

No.	Extinction coefficient.	
	A	B
1	0.350	0.344
2	0.308	0.305
3	0.173	0.172
4	0.179	0.181

The investigations prove the reliability of the separation.

3. The determination method employed is based on the method for andrin analysis originally found by Zimmermann (45, 46). A number of authors have used electro-photometers of different types as instruments for registration and have, for this purpose, modified Zimmermann's method. Zimmermann employs a Stufen photometer for measurement. The quantity and concentration of the reagents included in the reaction vary greatly with different authors. Friedgood and Berman (19) declare the necessity of uniformity with regard to the determination methods, in order to obtain comparable results from the different investigators. There is, at present, no method superior to all others. The modifications performed lately have not offered any particular security.

The present author has modified Zimmermann's method in two respects. The first concerns the calculation of the andrin contents in the extract. Zimmermann presents an equation for this calculation which is the same as the one he found applicable to a photometric determination of solutions, containing a mixture of pure androsterone and creatinine. The constants contained in this equation are calculated for an androsterone-creatinine compound. However, since the benzol solution does not include any creatinine after separation, such a formula must be considered unsuitable. The benzol solution is, of course, not a pure solution of 17-ketones. In all probability, a number of impurities occur, affecting the course of the reaction. However, it is, as yet, unknown, in what manner this takes place, and which these substances are.

The present author has employed a standard curve for his calculations, based on the extinction values of pure androsterone solutions in different concentrations. The andrin quantity is expressed in »mg androsterone». However, this value in »mg androsterone» does not denote that the urinary extract contains the stated amount

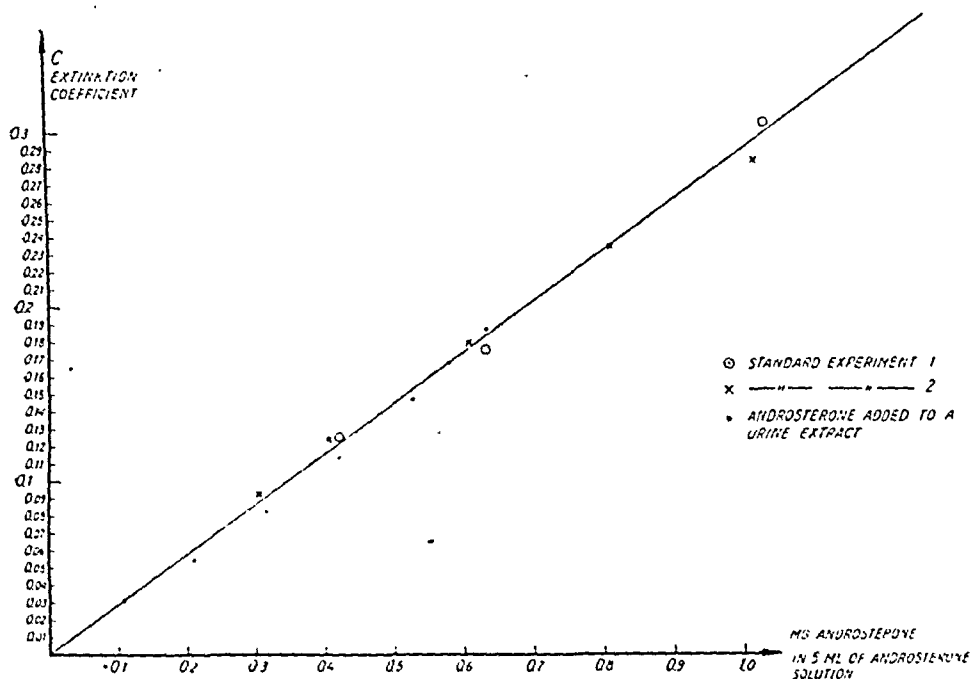


Fig. 1.

of pure androsterone. The andrins occurring in the urine give an identical colour intensity, with dinitrobenzene and alkali, to the amount of androsterone.

The results of two series of standard tests are introduced in the curve (fig. 1). In addition, a test series has been inserted, in which varying quantities of pure androsterone have been added to a urinary extract. Then, the extinction coefficient of the urinary extract has been determined, as well as that of the extract with the added androsterone quantities. From the values obtained, the extinction coefficient of the added androsterone may be calculated. This series lies comparatively close to the standard series.

Investigations performed by Callow et al. (9), show that the commercial m-dinitrobenzene affects the course of the reaction, owing to its contents of impurities. Therefore, Callow proposes a further washing and recrystallizing of the dinitrobenzene, according to a procedure related above. The present author has made parallel andrin analyses, partly with the original dinitrobenzene (column A in the table), and partly with the recrystallized substance (column B).

From this test, it will be seen that the dinitrobenzene should be washed and recrystallized before use.

Table 2.

No.	A mg	B mg	Difference A—B in %
1	45.5	46.5	— 2.2
2	47.3	48.0	— 1.5
3	59.8	51.4	14.0
4	8.4	7.5	10.7
5	71.2	70.0	1.7
6	45.0	42.4	5.8
7	38.8	31.1	9.5

In most cases, the benzol extract has a comparatively strongly saturated red or brownish red colour. Since the colour of the reaction compound is also red or brownish red, the present author has considered it suitable to test the degree to which the substances, which give the extract its colour, also affect the course of the reaction. For this reason, parallel analyses have been performed, partly of the original extract (column A in table 3), and partly of a portion of it which was first decolorized with *carbo animalis*, in a way described earlier (column B).

Table 3.

No.	A mg	B mg	Difference A—B in %	No.	A mg	B mg	Difference A—B in %
1	23.3	21.1	9.4	10	39.9	32.1	19.5
2	61.2	60.3	1.5	11	86.0	78.0	9.3
3	24.0	22.1	7.9	12	71.7	67.8	5.4
4	47.2	46.1	2.3	13	9.7	8.5	12.4
5	34.1	30.3	8.2	14	24.4	21.3	4.5
6	67.7	60.2	11.1	15	38.1	35.8	6.0
7	41.8	40.8	2.4	16	57.7	48.2	16.5
8	32.4	31.5	2.8	17	43.2	37.2	11.5
9	46.8	41.7	10.9	18	9.8	8.8	10.2

In order to control whether the *carbo animalis* absorbed the andrins occurring in the solution, a definite amount of pure androsterone was added to the benzol extract. The extract was then analysed, before and after treatment with *carbo animalis*, giving the following results (see Table 4).

Table 4.

No.	Ciba androsterone added.	Determined value	
		before absorp.	after absorp.
1	10.6 mg	11.2 mg	10.8 mg
2	9.3	8.9	9.1
3	10.1	9.3	9.3
4	10.2	9.7	9.4

By means of treatment with a small quantity of carbo animalis, the colour of the extract is eliminated which interferes rather considerably with the colour reaction at the analysis. However, the added carbo animalis does not, apparently, absorb the andrin component in the extract.

The reliability of the analytic method has also been tested in the following manner.

1. A weighed amount of androsterone has been added to the benzol extract solved in alcohol. By means of analysis, the quantity of added ascertainable androsterone was established.

Table 5.

No.	A Ciba androsterone added mg	B Determined value mg	Difference A—B %
1	10.0	9.2	8
2	9.5	10.5	—10.5
3	9.8	10.7	— 9.2
4	9.7	9.4	3.1
5	15.0	15.5	3.3
6	10.2	10.4	— 2.0

2. After hydrolysis, the urinary quantity was divided into two equal parts. To one part a weighed amount of pure androsterone was added. After extraction and analysis, the following values were obtained (Table 6).

3. The mean errors of the method have been determined in the following way. After hydrolysis, the urinary amount was divided into two equal parts, and the andrin contents in each of the tests were determined.

The following values were obtained (see Table 7).

Table 6.

No.	A Ciba androsterone added mg	B Determined value mg	Difference A—B %
1	10.6	11.2	—5.7
2	9.3	8.9	4.3
3	10.1	9.3	7.9
4	10.2	9.7	4.9

Table 7.

No.	Andrin content in mg.		Difference B—A (d)	No.	Andrin content in mg.		Difference B—A (d)
	A	B			A	B	
1	26.6	26.2	—0.4	11	30.7	28.7	—2.0
2	24.4	23.1	—1.3	12	32.2	25.3	—6.9
3	23.8	22.1	—1.7	13	20.2	16.7	—3.5
4	16.4	15.1	—1.3	14	19.7	20.4	+0.7
5	29.5	29.2	—0.3	15	20.3	19.5	—0.8
6	19.6	22.6	+3.0	16	14.1	19.1	+5.0
7	37.1	39.4	+2.3	17	15.1	14.3	—0.8
8	13.0	12.8	—0.2	18	24.4	23.9	—0.5
9	37.0	37.2	+0.2	19	11.1	12.0	+0.9
10	38.3	39.2	+0.9	20	20.4	19.9	—0.5

Difference $B - A = d$

Mean difference $\bar{d} = \frac{S(d)}{n} = \frac{-7.2}{20} = -0.36$ (1).

Standard deviation of difference: $\sigma_d = \pm \sqrt{\frac{S(d^2)}{n-1}} = \pm 2.45$ (2).

Standard error of mean difference: $\epsilon_{\bar{d}} = \frac{\sigma_d}{\sqrt{n}} = \pm \sqrt{\frac{S(d^2)}{n(n-1)}} = \pm 0.546$ (3).

Mean difference $B - A = \bar{d} \pm \epsilon_d = -0.36 \pm 0.546$ (4);

Standard deviation of a single determination: $\sigma_s = \frac{\sigma_d}{\sqrt{2}} = \pm 1.73$ (5).

Variation coefficient: $V = \frac{100 \times \sigma_s}{\bar{A}} \left(\text{där } \bar{A} = \frac{S(A)}{n} \right) = \frac{100 \times 1.73}{23.70} = 7.30\%$ (6).

It is clearly seen from above that there exists no systematic difference between the two determinations of one and the same sample. This fact enables us to use the formula (1). — (6) already quoted.

Correlation of photometry and biological assay.

A number of authors have compared the results gained at parallel photometric and biological analyses. Callow et al. (9), found comparatively good agreement and were, also in a position to state this circumstance in an equation. Also Furuhjelm (21) found a satisfactory correlation.

The material, submitted to investigation in the above-mentioned comparative analyses, was very heterogeneous. Alternately, healthy men, and women, and patients suffering from diseases in the glands producing andrins were included. Such a patient material is, however, not exactly suited for investigations of this kind. Later inquiries (see above) have revealed that the andrins, ascertained in the urine, appear in varying quantities with regard to healthy men, healthy women, and persons of both sexes with diseases in the gonades and the adrenal cortex. In addition, since the different andrins have a varying biological activity, a comparative investigation, between the photometric and the biological method, should take place in a homogeneous material. It would be suitable to choose healthy men or — though, not simultaneously — healthy women within a certain age category, since, in the higher ages, variations in the sexual gland insufficiency become prominent.

The investigations performed by the present author concern seven healthy men within the age group 20—30 years. The material is, unfortunately, too restricted for statistical analysis. No detailed account is given here of the biological determination method employed. Reference is made to Bomskov's »Methodik der Hormonforschung». However, the test methods will be related in brief.

The cocks employed as test animals were castrated at the age of eight weeks. Three months later, they were administered an injection of 2.5 I. U. androsterone. They could then be used in tests every fifth-sixth week. By injection of varying amounts of androsterone standard in sesam oil, a dose-response curve was obtained for each animal, from which the biological activity of the examined extract could be registered.

After the photometric analysis of the andrins, the rest of the urinary extract was solved in a definite amount of sesam oil. Each test animal was injected with 0.5 ml of oil solution five days running, thus obtaining 2.5ml in all.

At each test, the maximum length (L) and height (H) of the cock'scomb were measured. The sum of $L + H$ was allowed to serve as a standard of the size of the comb. The size of the comb was also measured on the sixth,

seventh and eighth test day. The percentage increase of the size of the comb is a standard of the biological activity of the preparation.

Each extract was tested on three cocks. A value of the activity of the extract was obtained for each of the test animals. The mean figure of these values was determined. The results are set forward in the table below (table 8):

Table 8.

No.	Photom. analysis mg androsterone	Biol. analysis I.U. androsterone
1	16	39
2	21	52
3	26	72
4	27	76
5	33	107
6	34	98
7	36	141

The correlation between the urinary contents of 17-ketones and biologically active substance, which is disclosed in the above-mentioned seven experiments, corresponds to the good results attained by Calow et al. (9), and Furuhjelm (21).

The andrin excretion in healthy men and women.

The present author has employed the method described above in an investigation of the andrin excretion in healthy men and women. Some of the test persons constituted patients treated for fractures, back insufficiency, ulcer, etc. who were examined at a time when they had, on the whole, recovered from their illness.

The analyses are performed on a quantity of urine corresponding to 48 hrs. The number of these tests in each case, submitted to examination, is stated in the table.

From the Table, it will be seen that also women excrete considerable quantities of andrin. Nevertheless, they do not excrete as much as men. This interesting fact has long been known. By means of the method employed by the present author, larger amounts have been ascertained in proportion to that found by other scientists. Holtorff and Koch (29) have found, in their material, an upper limit value of 18.9 mg per 24 hrs. in healthy men. Three healthy women excreted 21.7, 23.0 and 47.3 mg andrin, respectively. Drips and Osterberg (16) state figures of the same

Table 9.

A. Men.

No.	Age	Number analyses	Mg/day mean value.	No.	Age	Number analyses	Mg/day mean value
1	16	2	15.5	13	35	1	35.4
2	22	2	19.8	14	36	2	22.7
3	25	2	27.0	15	37	2	32.7
4	26	8	32.9	16	43	3	23.1
5	26	20	24.0	17	48	3	34.9
6	28	1	43.1	18	56	1	24.8
7	29	2	24.4	19	58	2	29.0
8	29	2	35.9	20	59	3	23.2
9	29	1	24.8	21	59	2	19.8
10	31	2	28.7	22	71	2	14.3
11	33	1	27.5	23	82	6	18.6
12	33	1	20.9				

B. Women.

No.	Age	Number analyses	Mg/day mean value
1	17	1	13.4
2	22	1	12.4
3	25	1	19.8
4	30	1	13.0
5	30	1	17.4
6	37	1	23.1
7	38	1	14.0
8	45	4	14.7
9	50	1	17.9
10	60	1	16.4

order of magnitude. Callow et al. (9), as well as Friedgood and Whidden (20) mention limit values in healthy men and women of 15 and 13 mg, respectively. These authors have made use of other modifications of Zimmermann's original determination method. Unfortunately, a direct comparison between the results gained with the different determination methods is, therefore, impossible.

An altogether reliable and simple andrin determination method

is, as yet, lacking. So long as this continues, each method, or modification of it, must be tested and its reliability established, before use.

In a material where the andrin excretion of the patients is subjected to examination, it is necessary to compare the results with the values obtained in healthy individuals. The result is, then, not to be regarded as an isolated numerical value, but should be judged in connection with the clinical picture. Moreover, the great variations in the andrin excretion in healthy individuals and, also, in one and the same person from one day to another, should be kept in mind. Repeated analyses afford greater certainty with regard to the results. Furthermore, they form a prerequisite for a scientific treatment of a material dealing with andrin excretion.

The andrin excretion in disturbances in the function of the sexual glands and the adrenal cortex.

The testosterone formed in the testicles is transformed to androsterone and etiocholan — 3 (a) ol — 17 — on, before being excreted with the urine. However, also castrated men excrete andrin, even though this occurs in smaller quantities than in healthy persons [cp. Hansen's (26) literature]. As already emphasized, also the adrenal cortex takes part in the andrin production in men. The andrins formed in the adrenal cortex are, in all probability, transferred to transdehydro-androsterone before being excreted.

It has been possible to prove that the andrins in women, for the most part, derive from the adrenal cortex. A few investigators believe themselves to have found that also the ovaries produce andrins [Parkes (40), Deanesly (12), Hill (27)]. Later, even castrated women have disclosed considerable excretion of andrins [Bingel (1), Dingemanse et al. (13), Luft (34)]. Hirschmann (28) performed quantitative and qualitative andrin analyses on the urine of healthy and castrated women. He found the same andrins and equal amounts of them in the urine from both categories. Furuhjelm (21) was in a position to detect the same quantities of andrin in the urine of two women, before and after castration.

In cases with virilizing tumours in the adrenal cortex, it has been possible to isolate strongly increased amounts of andrin in the urine. Broster and Vines (2) have been able to ascertain the occurrence of red-coloured granules in the tumour cells in these instances.

by means of a special colouring method (Ponceau-fuchsin). When no tumour was found, these granules occurred in the cells of the cortex. The reaction was negative in healthy individuals. The same authors state that the andrin production is localized to these cells.

It will be seen, from this summary account, that andrin determinations should be of diagnostic value in the following states of disease, viz., in females and children with hyper- or hypofunction conditions in the adrenal cortex, and, possibly, in males suffering from testis insufficiency. On the other hand, from a theoretical point of view, it should not be possible to diagnose cortical insufficiency in men, provided testis insufficiency does not occur simultaneously. Hyperfunction conditions in the cortex are exceedingly rare among men and are, therefore, of minor importance in the present discussion.

In the following, the present author will give an account, in brief, of a few cases in which the andrin analyses proved of diagnostic value, or, otherwise, contributed to illustrating what has been said above.

Testis insufficiency.

Case no. 1. Male, 57 years old. Genital hypoplasia since childhood. Height 195 cm, stretch from one fingertip to the other 210 cm. Typical eunuchoid habitus with long extremities and a broad feminine pelvis. Distinct mons veneris, adipose mammae. No hair on the pubis or in the axillae, no growth of beard. The right testis not palpable, the left, the size of an almond. Penis appr. 1 cm. long. The skin pale yellow, thin and wrinkled. The voice shrill.

Andrin determination: 12.6, 6.6, 15.5 mg/24 hrs.

Treatment with hypophysis anterior lobe extract (Ambinon) 7/10—6/11 1940, an ampulla every other day. *Andrin determination under treatment:* 18—20/10 18.6 mg, 20—22/10 19.3 mg, 22—24/10 22.9 mg, 25—27/10 24.1 mg/24 hrs. However, no subjective or objective improvement. Better after the addition of 25 mg testosteronepropionata daily. Vitality greater. Penis increased in size. The pat. began to show an interest in the opposite sex.

Case no. 2: Male, 46 years old. Formely healthy and with a normal sex life. Since 1937, in connection with a joint affection, rapidly progressing testis atrophy and impotency. Total loss of hair on the pubis, the axillae, the trunk and the extremities. Testes the size of biggish hazelnuts. Penis not quite 2 cm long. No erection capacity. But slight growth of beard. B. M. B. — 15 %—34 %. Cholesterin in the serum 322 mg %.

Andrin determination: 6.4, 6.0, 1.3 mg/24 hrs.

Treatment: Pregnyl 1 amp. at 600 R. E./4 days. Subjective improvement after 4—5 injections. Objectively: Increased growth of beard, also growth of hair on pubis and the extremities. Erection a few times. Testis and penis increased in size. Reduction of the adipose layer on the trunk.

Andrin determination during treatment: 10.0, 9.5, 11.7 mg.

Case no. 3. A young man, 19 years old. Prepuberal habitus. No growth of beard and no hair on the trunk. Testes the size of half a hazelnut. Penis appr. 1 cm long. Comparatively broad pelvis. Height 178 cm, stretch from one fingertip to the other 187 cm. B. M. B. — 7 %.

Andrin determination: 12.4, 11.6 mg.

Treatment with gonadotropin (Pregnyl) without definite effect.

Earlier investigations of the andrin excretion in conditions of insufficiency in the testis have offered varying results. Some authors have declared themselves unable to ascertain any andrin excretion in cases of eunuchoidism [Mc Cullagh et al. (36, 37), Kochakian (33), Feinier et al. (18)]. However, others have shown considerable quantities of andrin in the urine in such cases [Bingel (1), Koch (31, 32), Kenyon et al. (30), Hansen (24, 25), Mc Cullagh et al. (36), Callow et al. (10)]. The endocrine function of the testis cannot be directly judged by means of andrin analysis, on account of the extragonadal development of some andrins. The results from andrin analyses on cases of eunuchoidism must be compared with the andrin excretion in healthy men. In the three cases, related above, a distinct reduction of the andrin excretion occurred. In one of the cases, in which the condition had lasted only for approximately 3 years, the andrin excretion was lesser than in the two others, where the insufficiency had lasted during the whole of their lives. This corresponds with results obtained by Hamblen et al. (23). These investigators have been in a position to show, by means of andrin determinations, that the andrin production of the adrenal cortex compensates the reduction or termination of the andrin production in the testis of older men and castrates.

The supply of gonadotropic hormone seemed to have a stimulating effect on the andrin excretion in two of the above-mentioned cases.

Morbus Addison:

Case no. 1. Female, 32 years old. For one year, pigmentation on the trunk and mucous membranes, grew thin, increasing asthenia. Blood

pressure: 140/85. Blood sugar 98 mg %. Blood chlorides 320 mg %. Potassium in the serum 23—26 mg % (normal value 17—21).

Andrin determination: 14.8, 14.8, 18.6, 18.2 mg/24 hrs. A month later acute Addison crisis. *Andrin determination* after the patient had recovered: 4.9 and 4.0 mg. She was administered Cortin DOCA and rapidly improved. The adynamia disappeared, the pigmentation became paler, her appetite improved and she increased in weight. Blood pressure, blood sugar and electrolytes in the blood showed normal values. In spite of this, further reduction of the *andrin excretion:* 2.1, 1.9, 3.5, 4.8 mg. Discharged in good condition, but neglected her medicine, and died about a month later. No adrenals were found at autopsy: the microscope revealed no adrenal tissue on the place of the adrenals.

Case no. 2. Female, 39 years old. During the last months, brown pigmentation spots on the trunk and mucous membranes, increasing adynamia, loss of appetite and weight. Diarrhoea and vomiting. Blood pressure 90/60. Blood sugar 66 mg %. She was regarded as a case of morbus Addison and treated with Percorten, Cortin DOCA, sodium chloride and bicarbonate. She improved considerably. *Andrin analysis* at this stage: *andrin excretion stopped*. Then again deterioration and death. Autopsy revealed extensive tbc, caseous necrotic masses being substituted for the adrenals.

Case no. 3. Female, 23 years old. During the last years, pigmentation of the skin and mucous membranes. During the last months, increased asthenia and loss of weight. In April, 1940, acute Addison crisis, unconscious, blood pressure not measurable, blood sugar 68 mg %, temp. 39°. Improved after DOCA treatment. In October, 1940, implantation of 5 tabl of 50 mg DOCA each. Repeated periods of deterioration in her condition. More intense specific treatment was then given. *Andrin determination* was performed during a period when the patient was in very good health and the values 9.8, 5.2, 7.6, 5.1 mg/24 hrs. were obtained.

Case no. 4. Female, 28 years old. During the last year, increased feeling of tiredness and loss of weight. Vomiting and diarrhoea. Insignificant brown pigmentation only on the trunk. She was admitted in a precomatose state with blood pressure 80/60, blood sugar < 50 mg %, blood chlorides 288 mg %. Rapid improvement with DOCA, sodium chloride and glycose. Discharged fit for work. *Andrin excretion at discharge:* 3.1 and 2.5 mg/24 hrs., respectively.

Case no. 5. Female, 40 years old. She had suffered, during the last year, from increased loss of weight, tiredness, and dyspeptic troubles. Insignificant increase of brown pigmentation on the trunk. Blood pressure, blood sugar and electrolytes in the serum showed normal values. The diagnosis was uncertain. *Andrin analysis* on this occasion (July, 1941): 6.4, 19.6 and 11.3 mg/24 hrs. The patient improved with DOCA and sodium chloride. *Andrin analysis in August, 1941:* 2.0 and 4.2 mg, in spite of the fact that the patient was now in a better state than a month earlier. In September,

the andrin excretion equalled 3.0 mg, in November 1.7 and 0 mg. She died on Dec. 1. Autopsy revealed extensive bce with complete caseous degeneration of the adrenals.

In all the above-mentioned five cases of morbus Addison in females, an increased reduction of the andrin excretion was perceptible. Treatment with Cortin DOCA did not affect the andrin excretion, in spite of the considerable improvement in the condition of the patients occasioned by this treatment. This stands in opposition to the belief that a general chock effect at morbus Addison should be the cause of the reduced andrin excretion. Thus, Furuhielm (21) was able to ascertain a post-operative reduction in the andrin excretion. Moreover, the present author found greatly reduced andrin excretion in a few cases of malignant tumours with cachexia. In none of the above-mentioned cases of morbus Addison did cachexia or chock occur at the andrin analysis.

The results obtained support the belief that the adrenals take part in the andrin production [cp. also Luft (34), Callow et al. (10)].

Hyperfunction conditions in the adrenal cortex:

(These cases will be published later in more detail).

Case no. 1. Boy, 7 years old. During the last months, increasing apathy and gain in weight (7 kg). Beginning growth of hair on the pubes. The disease picture was comparatively lacking in symptoms. After an attack of unconsciousness the patient was admitted to a hospital, a tumour being palpated to the left in the abdomen.

Andrin analysis: 155 and 132 mg/24 hrs., respectively. Operation disclosed an adrenal tumour, the double size of a first, with outgrowths. The microscope revealed a cancer of the adrenal cortex.

Case no. 2. Boy, 2 years 5 months old. At the age of 1 year and 9 months hair began to grow on the pubis, and the penis increased in size. The length of the body also increased and his physique became heavier. (At the exam. 105 cm long, and weighed 17.5 kg). Penis was the length of that of a child of 15 years, testis, being the size of shell-almonds, the length of that of a boy of 6.

Andrin analysis: 52.5, 24 and 41 mg/24 hrs., respectively. Ensuing operation revealed that the right adrenal was hardly of normal size, while the left one was approximately twice as large. The cortex showed considerable hyperplasia.

Andrin determination has acquired particular diagnostic importance in hyperplastic conditions in the adrenal cortex, at

adenoma and malignant tumours. An increased andrin excretion has been ascertained, which corresponds with the clinical picture in these cases, which discloses a more or less strongly pronounced increase in virility as its most prominent symptom. At present, no other morbid conditions with increased andrin excretion are known.

A number of authors have had the same experiences with andrin analysis in virilizing disturbances in the adrenal cortex [cp. Kenyon et al. (3), Crooke and Callow (11)]. The results distinctly disclose the capacity of the adrenal cortex of producing andrins.

Summary.

The present author renders an account of the physiology of the androgenic substances and their excretory conditions. The determination methods, occurring in the literature, as well as the justification and clinical significance of the hormone analyses, have been subjected to discussion. The chemical analytical methods were found to be distinctly superior to the biological ones. Above all, they form a standard for the total andrin excretion, and do not only measure the occurrence of biologically highly active substances. In his investigations, the present author has employed a modification of Zimmermann's original method for andrin determination. He gives a report of the investigations performed in order to ascertain the reliability of the method. The andrin excretion of 18 healthy men and 10 healthy women has been determined. The results revealed a comparatively small distribution within the two groups.

The clinical applicability of andrin determination has been discussed. Earlier andrin determination and experimental investigations on animals have shown that, in all probability, the adrenal cortex plays a part in andrin production. Apparently, most of the andrin production in women is carried out by this organ. The investigations performed by the present author, of the andrin excretion in cases of testis insufficiency, morbus Addison and tumours in the adrenal cortex, support this contention.

In three cases of testis insufficiency or total termination of the testis function, the andrin excretion was greatly reduced but, nevertheless, had not altogether ceased. In two of the cases, a

stimulation of the andrin excretion could be occasioned by a supply of gonadotropic hormones.

In five cases of morbus Addison, in women, an increasing reduction of the andrin excretion was ascertainable. The reduction progressed in spite of treatment with Cortin DOCA which considerably improved the condition of the patients.

This must have been due to an increasing destruction of the adrenal cortex. Three of the cases died and an autoptical examination revealed complete destruction of the adrenals.

Furthermore, the author describes two cases of hyperplastic changes in the adrenal cortex. One of these instances had a diffuse hyperplasia of the cortex in one of the adrenals, the other a cancer proceeding from the adrenal cortex. Both of them occurred in young boys, causing a premature development of the secondary sexual characteristics. In both cases the andrin excretion was greatly increased.

The related cases illustrate also the clinical significance of the determination method.

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Continued Investigations on Histamine in Faeces.

By

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(Submitted for publication July 2, 1943).

In a previous joint work with J. Tomenius the writer has described how considerable quantities of histamine can sometimes be found in the faeces of asthma patients. While only quite small quantities of histamine, 0—4 γ pr. cm^3 , were found in the faeces of healthy subjects with our method, considerable quantities, in one case more than 250 γ pr. cm^3 , were found in the faeces of asthma patients.

In this work the results of continued investigations are presented concerning the histamine in faeces.

Method.

In these experiments the author has mainly followed the method that was adopted and circumstantially described in the previous work. This method is an application of Barsoum & Gaddum's well known one. A volume of 10 cm^3 faeces is carefully mixed with 40 cm^3 10 % trichloroacetic acid and should stand for at least 2 hours, after which it is centrifugalized and filtered. The filtrate is then extracted by means of ether to neutral reaction for Congo red, after which a sufficient quantity of 10 n HCl is added to make the mixture 2 n. It must then boil for 2 hours, be evaporated to dryness, after which the remainder is dissolved twice in 95 %

alcohol and evaporated to dryness. The remainder is dissolved in 15 cm³ 98.5 % alcohol, filtered and evaporated for storage for any length of time. When the extract is titrated, it is dissolved in 3 cm³ aq. dest., neutralized with 0.1 n NaOH and filtered. The titration is carried out on the surviving intestine (ileum) of a guinea-pig, which is hung up in 37° Tyrode solution, and this is supplied with oxygen mixed with 5 % carbon dioxide. The vessel in which the intestine was hung held ca 25 cm³, and in this liquid the intestine usually reacted to 1—2 γ . In the previous investigation carried out by Tomenius and the writer a vessel holding only ca. 9 cm³ was used, and then the intestine generally reacted to 0.1—0.2 γ . The writer found it more convenient, however, to work with the larger vessel, in spite of the method thus becoming somewhat less sensitive. This is probably the reason why the number of entirely negative histamine tests are greater in this series than in the former one.

It has not been the routine method to atropinize the intestine. The writer shares Riessers doubts in this respect and has observed that even in concentrations of 1:2.5 mil. or 1:5 mil. atropine has at times a very inhibitory effect.

The method adopted calls for still further comment. Åkerblom has stated that when making use of Barsoum & Gaddum's method histamine could be obtained from any histidine that might possibly be found in the specimen. It is not clear from his paper whether he has taken into consideration a possible histamine effect in the untreated histidine solution. Tomenius and the writer have already devoted their attention to this question in the above mentioned work. We found, however, that the histamine effect was less in a histidine solution (ulcustin) after the B. & G. treatment than it was in the untreated solution. Emmelin, Kahlson and Wicksell also categorically reject the assumption that histamine is formed from histidine when using B. & G.'s method. The fact that the writer has been able to prove the existence of histamine in faeces by means of dialysis (to be discussed later on) also disproves the assumption that the histamine in faeces should develop during extraction.

The writer has gone into the question as to the quantity of histamine that can really be obtained by the method adopted. After making experiments by applying known quantities of histamine, Tomenius and the writer came to the conclusion that the loss went

up to 20—40 %. Further experience gives the writer reason to suppose that the losses are generally far greater. If histamine were added after faeces has been mixed with the trichloroacetic acid, i. e. at the beginning of the extraction process, 39 % would be recovered. If the histamine were added after the centrifugalization, filtration and extraction with the ether, 55 % would be recovered. If the addition were made still later, i. e. after the specimen has been boiled with the acid, 66 % would be recovered. Thus the losses are considerable. This means that the quantities of histamine found in faeces must at least be doubled, in order to obtain the quantity of histamine really existing.

The disappearance of histamine in faeces will be discussed later.

The writer has naturally taken into consideration the criteria that the substance obtained from faeces really is histamine. Apart from the criteria of Tomenius and the writer, i. e. the effect of the substance obtained on the atropinized intestine, its lowering effect on the blood pressure in cat, its capacity when given in large doses to inhibit the effect of a new dose of histamine, it may now be mentioned that the effect of the substance is entirely eliminated by thymoxydiethylamine¹.

It will therefore be beyond doubt that the substance obtained from the faeces really is histamine.

Dialysis Experiments.

It is of interest from many view points to investigate the possibility of obtaining faeces histamine by means of dialysis. From a few experiments carried out by Tomenius and the writer, it seemed as if the greater part of the histamine could be obtained by dialysis. Our object with these experiments was chiefly to illustrate the untenability of the assumption that the faeces histamine should be an artifact, brought about by means of the extraction process.

Dialytic experiments are, however, of interest in that they may offer a more convenient method than that of Barsoum and Gaddum, which is somewhat circumstantial. Moreover they are able to illustrate whether histamine exists in active form in faeces. Several investigators, among others Tarras-Wahlberg, Emmelin, Kahlson

¹ Professor Georg Kahlson has been kind enough to lend the writer assistance with this test.

and Wicksell have presumed that the histamine in the blood exists in a physiologically inactive form.

The dialytic experiments carried out by the writer were originally made in order to see whether it were possible to reach a more simple method for obtaining histamine. It proved impossible at first in numerous experiments to obtain histamine dialytically, and the writer found that a considerable amount of histamine must be destroyed in the dialytic experiments. This destruction will be referred to later. When the writer had learnt to take this into consideration and to avoid it as far as possible by dialyzing for relatively short periods, it was possible to obtain histamine from the faeces by dialysis.

Experiment. Faeces from patient B. H. A., who was suffering from serious asthma was divided into 3 portions, A, B and C, each of 10 cm³, and was treated in the following manner. Portion A was carefully mixed with 15 cm³ tap water and was then placed in a tube which was kept in water at 80° for two hours. It was then put for dialysis into a temporarily prepared collodium capsule, which was placed in a vessel containing 7 cm³ tap water. After 6 ½ hours the dialyzate was titrated and found to contain 19 γ histamine pr. cm³ which, assuming that the histamine had had time to become equally distributed, corresponds to an original faeces percentage of 60 γ pr. cm³. Portion B was also mixed with 15 cm³ tap water and then put for dialysis for 8 hours without previously going through any heating process. Titration in this case gave 13 γ pr. cm³ in the dialyzate, corresponding to 42 γ pr. cm³ faeces. Portion C was extracted in the usual way according to Barsoum and Gaddum and when titrated gave a histamine percentage of 20 γ per cm³.

In another experiment with faeces from the same patient cellophane was used as the dialytic membrane. 11 cm³ faeces were mixed with 34 cm³ tap water and put into a cellophane capsule, which was put into 15 cm³ water. The dialyzate was tested 6 ½ hours afterwards and was found to contain 4 γ pr. cm³ which, assuming that the histamine was equally distributed, corresponds to 22 pr. cm³ faeces. Part of the dialyzate was treated with extraction in the usual manner and the extract thus obtained gave 1.25 γ pr. cm³. Part of the original faeces specimen was treated with extraction and gave 14 γ pr. cm³ faeces.

From these dialytic experiments it thus seems evident that the faeces histamine when suitably treated can be obtained by means of dialysis, and that it is possible to obtain in reality greater quantities by this process than by extraction. The quantities obtained fairly well correspond to those that may be presumed

really to exist in faeces if a loss of 50—60 % is calculated in the extraction process.

Of course it must not be definitely assumed that the faeces histamine is to be found in an active form, as nothing is so far known of the sort of compound that would presuppose the inactive form of histamine in plasma. This dialytic procedure, too, might involve a sufficient injury to liberate the histamine from its hypothetical combination.

As the histamine in faeces can be obtained by means of dialysis, there is reason to suppose that given suitable conditions it might be possible to prove that there is a histamine effect in untreated faeces. The writer has also succeeded in proving such an effect with a faeces specimen from an asthma patient. 10 cm³ faeces was carefully mixed with 10 cm³ Tyrode solution. The suspension was properly centrifugalized and the centrifugate tested on the intestine preparation direct, and 2 cm³ gave a histamine effect corresponding to 3 γ , thus 1.5 γ pr. cm³. An ordinarily prepared extract gave a histamine effect corresponding to 2.7 γ pr. cm³ and a dialytic test gave 4—8 γ .

The Inactivation of Faeces Histamine.

Tomenius and the writer were interested to find out how long histamine would keep in faeces and we came to a fairly satisfactory conclusion. A faeces specimen from the asthma patient E, which on immediate examination showed a histamine percentage of ca. 100 pr. cm³, showed undiminished activity even after having been kept in room temperature for 48 hours.

When the writer began with dialytic experiments on a more extensive scale, it soon became evident, however, that histamine in faeces specimens mixed with water became largely inactivated or destroyed. Even if considerable quantities of histamine were added, the dialyzate proved only slightly active or else was quite inactive.

There may be several causes for this phenomenon. Koessler and Hanke have called attention to the fact that histamine is inclined to be absorbed into fine particles. The writer noticed that while histamine usually passes through a collodium membrane quite

easily, it was retained completely if charcoal were mixed in the solution:

The disappearance of histamine in dialytic experiments, however, cannot be entirely due to absorption. If faeces is heated previous to the dialysis, say for 2 hours in 80°, the loss of histamine is less, whereas it is much greater if the dialysis takes place at a temperature of 37° instead of that of a room.

It is therefore probable that a bacterial decomposition or possibly a disintegration due to histaminase must be taken into consideration. As histaminase is to be found in the mucous membrane of the intestine, it is not unreasonable to presume that the enzyme in question might exist freely in faeces. Those who have studied histaminase, however, maintain that it is an extremely delicate substance.

The writer's experiments have shown that the loss of histamine in dialytic experiments is considerably greater in 37° than in room temperature, whereas it only decreases slightly in + 5°. It decreases considerably when the specimen is heated to 80° for 2 hours and also when a strong acid is added; neither of these measures, however, checks the loss entirely. The writer is of opinion that these experiments show that several factors must influence the process. It is uncertain whether it is necessary to consider the existence of histaminase at all.

The Clinical Occurrence of Faeces Histamine.

In their above-mentioned work Tomenius and the writer originally intended to investigate whether there were possibly any histamine in faeces in *colitis ulcerosa*. This was scarcely proved to be the case. On the other hand a faeces specimen happened to be examined from a patient suffering from severe asthma, and a quantity of histamine was found to exist. The observation could be repeated, and increased histamine values in faeces were discovered in 5 of the 10 asthma patients examined.

In the series of experiments here reported on it has been possible to discover the phenomenon in 8 specimens out of 35 examined from 24 patients suffering from asthma bronchiale. Histamine has been found to exist in the severe cases, i. e. those who were in a status asthmaticus condition. In the slight cases on the other

hand there was little or no histamine. The writer has noticed that histamine appeared when asthma got worse and disappeared when it got better.

The discovery of histamine in an asthma patient, who apart from bronchial asthma was also suffering from heart failure with liver enlargement, made the writer examine the faeces from patients with cardiac diseases, and this led to the observation that also in these cases which are not of an allergic nature, histamine may be found in pathological quantities (the writer reckons with values of more than 5 γ pr. cm^3 faeces). Increased values were found in 5 specimens out of 21 examined from 16 patients. In one case there were no fewer than ca. 220 γ , the remaining 4 containing 60, 20, 6 and 6 γ respectively. The writer has endeavoured to judge what these cases could have in common (shortage of breath, liver enlargement etc.) but it has not been possible to fix anything definite. All the cases were serious, which is illustrated by the fact that three patients died while in hospital.

It is so far uncertain whether histamine in faeces occurs in other groups of diseases, as it has not been possible to investigate methodically a large amount of material. Out of 12 specimens examined from patients with different diseases and healthy subjects, 8 were entirely free from histamine, while the others had values of under 2 γ pr. cm^3 .

It is naturally possible that the existence of histamine in faeces may be a more common phenomenon than was at first supposed.

The Origin of Faeces Histamine.

When Tomenius and the writer first observed the existence of histamine in faeces in asthma patients, it was naturally presumed that the histamine had been formed in the contents of the intestine owing to the bacterial decarboxylation of histidine. Attention was devoted to colitis ulcerosa since Nanna Svartz had pointed out that in these cases enterococci, which are known to form histamine, often exist in abundance.

The bacterial effect has, moreover, often been resorted to in order to explain the appearance of histamine. Mellanby and Twort isolated from the intestine bacteria, which might form

histamine. Åkerblom considers that histamine, formed in the intestine owing to bacteria, causes the so-called lamellitis in horses. Knott and Oriel have isolated Gram-negative bacteria from the sputum of asthma patients and have indicated that there is a possibility of a histamine production in the breathing organs. The two latter investigators on the other hand found nothing abnormal in the faeces of asthma patients.

There is, however, a great deal to discredit the fact that histamine found in an increased quantity in faeces should be the result of bacteria. It seems a priori scarcely likely that asthma and certain cardiac patients should have special bacteriological conditions in their faeces. In the couple of hundred specimens that the writer has examined, these faeces have in no way appeared characteristic macroscopically but have offered specimens of various types of faeces occurring in clinics. In some cases the cultivation of faeces has been carried out and it has proved normal when tested in the usual manner. Even if a bacterial genesis cannot of course be entirely excluded, there will be reason to discuss other causes of origin than the bacteriological ones.

As it has been proved by Knott and Oriel and subsequently by Riesser that asthma sputum can contain histamine, the possibility of the histamine in faeces originating from swallowed sputum must be considered. This seems, however, extremely unlikely. The explanation, moreover, is untenable as regards cardiac patients and it is equally impossible to explain the histamine in asthma patients in this manner, as the histamine in sputum will occur in such small quantities that liters and liters would be required of the sputum swallowed in order to produce the quantities found by the writer. With regard to this question the writer bases his opinion on the values for the sputum histamine that Riesser has presented in his work. In the few cases in which the writer has himself examined the sputum, it has not been possible with the method in question to prove the existence of any histamine at all either in asthma or in purulent sputum from a patient suffering from bronchiectasis.

As a third hypothesis the question of a histamine excretion to the intestine must be considered. Later researches have shown that under certain conditions histamine is liberated from the tissues. Dragstedt has shown that histamine is liberated from the liver

in anaphylactic shocks in dogs. Emmelin, Kahlson and Lindström have shown that histamine is liberated from the skin of guinea-pigs under anaphylactic reactions. Tarras-Wahlberg has shown that the skin of rabbits and cats give off histamine when treated with ultra violet rays. In such circumstances it seems possible that under status asthmaticus or in the event of serious heart failure there might be postulation for a liberation of histamine perhaps from the mucous membrane of the intestine, perhaps from the liver, and that it is this histamine that can be demonstrated in faeces. At present, however, the writer cannot support this hypothesis with any direct experiments.

Summary.

1. The writer has studied more closely the phenomenon which Tomenius and he have already described, that histamine may sometimes be proved to exist in the faeces of asthma patients.

2. This histamine can be obtained from faeces by means of dialysis and a histamine effect has been directly observed even in a suspension of faeces.

3. The faeces histamine undergoes an inactivation in diluted faeces, which cannot be entirely explained by absorption but which is probably caused by destruction due to bacterial influence.

4. The faeces histamine occurs clinically in severe cases of asthma bronchiale but has also been proved to exist in cases of heart failure.

5. Consideration must be taken to the possibility that the histamine in faeces may originate not only from bacterial influence in the contents of the intestine but also from excretion to the intestine.

For this investigation I have received financial help from the Medical Clinic of the Serafimerlasarettet and also from »Konung Gustaf V:s 80-årsfond», for which I beg to express my sincere gratitude.

Finally, I should like to thank Miss Dorothy Ferris who has carried out the translation.

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REVUE DES LIVRES.

W. Heupke: Die Faeces des Menschen. 2. Aufl. (Bd. 28 von Medizinische Praxis, herausgegeben von Grote, Fromme, Warnkros, Lange) Dresden u. Leipzig, Verlag Steinkopff. 115 S., 1943. Preis: geh. RM 12: —, geb. RM 13.50.

Eine sehr gute Darstellung, in der Hauptsache für den praktischen Arzt gut abgepasst. Einzelne Teile sind jedoch unnötig, weil für den praktischen Arzt nicht brauchbar und ohne Interesse für praktische Diagnostik und Therapie. Als solche bezeichne ich die ausführliche Darstellung der Methoden für quantitative Bestimmung im Stuhle von z.B. Urobilin und Urobilinogen, Stickstoff, Fett, Zellulose u.s.w.

Das letzte Kapitel: »Die Deutung der Stuhlbefunde«, wo die allgemeine klinische Erfahrung des Verf. zu Worte kommt, finde ich ziemlich schwach. Bei Besprechung der bei Achylie vorkommenden so genannten gastrogenen Durchfälle bemerkt Verf., dass sie nicht in allen Fällen von Achylie auftreten und dass man daher für ihre Entstehung »Hilfsursachen« in Betracht ziehen muss. Eine solche glaubt er in ungenügender Sekretion des Pankreassaftes zu finden. Da die Durchfälle bei Achylie immer nur episodisch auftreten, scheint auch diese Erklärung ungenügend. Auch die Gärungsdyspepsie zeichnet sich unter anderem durch oft auftretende leichtere Diarrhoeen aus und kommt ebenso vorzugsweise bei Achylikern vor. Überhaupt scheint mir der Begriff gastrogene Diarrhoeen unklar und nicht von den mit gärungsdyspeptischen Phaenomenen verlaufenden Zuständen zu unterscheiden. Dem Verf. scheint es nicht bekannt zu sein, dass durch in dieser Zeitschrift veröffentlichte Arbeiten von mir klargelegt wurde, dass die s. g. Gärungsdyspepsie durch eine bakterielle Darminfektion her-

vorgerufen wird, die chronisch unter akuterer Schüben verläuft und allmählich zu einer bei der romanoskopischen Untersuchung und später auch röntgenologisch konstatierbaren Colitis führt. Meine Schülerin Prof. Dr. Nanna Svartz hat dieser Frage ein eingehendes Studium gewidmet, die Erreger reingezüchtet und damit experimentell eine typische »Gärungsdyspepsie« hervorrufen können. Zweifelsohne ist die Pathogenese der »gastrogenen Diarrhoeen« eine ähnliche.

I. Holmgren.

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The abnormal electrocardiogram.

II. New Criteria of Right and Left Axis Deviation.

By

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Ever since the earliest days of electrocardiography a particular configuration of the QRS complex has been designated as left ventricular preponderance or, preferably, left axis deviation: a large R_I in connection with a large S_{III} . Correspondingly, another configuration — large S_I together with large R_{III} — has been designated as right ventricular preponderance or right axis deviation. From such electrocardiograms to normal, however, there is a gradual transition, and hence it has been necessary to set up more precise limits for right and left axis deviations. Hitherto this has been done by employment of two procedures: determination of Einthoven's $< \alpha$, or calculation of special indices.

In the present work a critical review will be given of the methods employed so far for delimitation of the right and left axis deviations. Then, on the basis of a new conception of the axis deviation, an account is given of some new criteria of the right and left axis deviations which the writer thinks are particularly suitable for clinical use.

The determination of the $< \alpha$ for the electric axis was introduced by Einthoven. In order to find a rule for, and give an explanation of, the changes in size presented by the deflections in the three derivations from the extremities under certain conditions as

forced respiration and postural changes of the body, Einthoven schematized the human body as follows: The human body is represented by a flat, homogeneous, conducting plate in the form of an equilateral triangle RLF (Fig. 1) in which R corresponds to the right shoulder, L to the left shoulder and F to the left foot, that is, RL corresponds to Lead I, LF to Lead III and RF to Lead II. The heart is imagined to be placed in the center of gravity of the triangle, and its size to be very small in proportion to the length of the sides of the triangle. Supposing now that in the heart a potential arises in the direction of the arrow and of the magnitude pq , the deflections from the corners of the triangle in the three derivations will have the

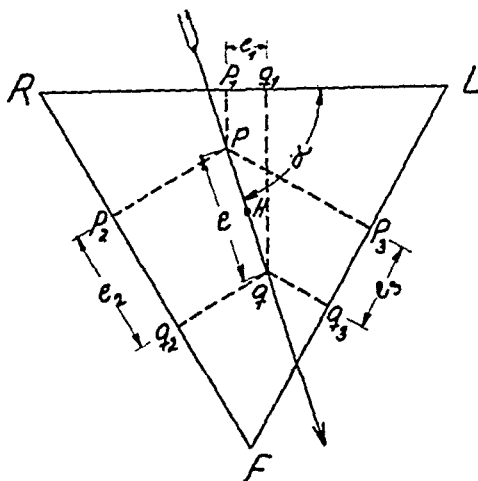


Fig. 1. Schema for the electrocardiogram. For explanation, see the text. (After Einthoven, Fahr & de Waart, 1913, Fig. 22.)

magnitude of p_1q_1 , p_2q_2 and p_3q_3 . Conversely, if p_1q_1 , p_2q_2 and p_3q_3 represent the respective magnitude of the deflections in the three derivations, these deflections must result from the potential in the heart with the direction angle α and the magnitude of pq . From Fig. 1 it will be noticed that $e_1 = e \cos \alpha$, $e_2 = e \cos (\alpha - 60^\circ)$ and $e_3 = e \cos (120^\circ - \alpha)$. These equations give

$$\operatorname{tg} \alpha = \frac{2e_2 - e_1}{e_1 \sqrt{3}}, \operatorname{tg} \alpha = \frac{2e_3 + e_1}{e_1 \sqrt{3}} \text{ and } \operatorname{tg} \alpha = \frac{e_2 + e_3}{(e_2 - e_3) \sqrt{3}}, \text{ which}$$

shows that α can be calculated when the size of the deflections in two of the leads is known. α is recorded in degrees, and designated as positive in the direction from L over F to R (that is in the two quadrants, I and II, below the horizontal line RL), and negative from L over a point above RL, symmetrical with F, to R (that is, in

the two quadrants, IV and III, above the horizontal line). $\angle \alpha$ gives the direction of the potential that is active at the given instant, or the resultant of the active potential at this particular juncture. e gives the value for the active potential and is designated by Einthoven as the manifest potential. e can be calculated from the first set of quotations when $\angle \alpha$ and the size of the deflection in one of the three derivations are known.

Obviously, for each point in the electrocardiogram there must be a resultant in the Einthoven schema as the one shown in Fig. 1. But in the question about the right or left axis deviation Einthoven was interested only in one of these resultants — namely, the resultant corresponding to the apex of the most important (*i. e.*, the greatest) wave in the QRS complex. Einthoven stated that $\angle \alpha$ for the electric axis in normal subjects varied between $+40^\circ$ and $+90^\circ$, but subsequent investigations have shown these limits to be too narrow. From the investigations reported by Proger & Davis, Hoskin & Jonescu and Kaj Larsen & Skúlason, it is to be expected that the electric axis in about 95 % of all normal subjects will fall between 0° and $+90^\circ$. It is reasonable, therefore, to designate this range of variation as the normal, and positions of the axis outside this range as respectively left and right axis deviation.

In recent years several investigators have looked into the question whether the schematization of the human body as performed by Einthoven is warrantable (Wilson, McLeod & Barker; Koch-Momm; Koch; Fröhlich; Hollmann & Hollmann). That there have been good reasons for such investigations is obvious when we consider the contrast between the presuppositions adopted by Einthoven and the actual conditions: The human body is not a two-dimensional but a three-dimensional structure; it is not a homogeneous conductive mass but a non-homogeneous mass of tissues differing in conductivity; and the heart is not infinitely small in relation to the three sites of derivation. Furthermore, the distance of the heart from the three sites of derivation is not the same, the heart lying nearer the left shoulder than the right shoulder and the left hip. Indeed, the aforementioned investigators have shown that on the basis of the Einthoven principles we may obtain only a very incomplete insight in the actual electrical conditions in the heart. Still, it seems warrantable, for instance, to assume that a majority of the potentials (dipoles) will be orientated in about the same

direction as the resultant determined after Einthoven. In this connection it is to be emphasized explicitly that the criticism advanced does not apply to the justification of entirely empirical ways for enquiry into the relations between various changes in the heart and different positions of the electric axis of Einthoven. But, it is quite possible indeed that these questions may be solved more rationally once the electrical conditions in the heart become fully elucidated.

For clinical purposes it is practical to have tables from which the degrees of $\angle \alpha$ can be read when the direction and size of the deflections in at least two derivations from the extremities are known. Such tables have been given by Einthoven, Fahr & de Waart and, later, by Sabena and Plenzner. It may be of advantage also to make use of various diagrams, which are all based on the same principle as is employed in the geometrical construction of the vector cardiogram (see below). Such diagrams were given first by Carter, Richter & Greene and Dieuaide. A particularly practical elaboration of such a diagram is v. Zarday's axonometer.

In practice we meet with various difficulties in the determination of $\angle \alpha$. The rule laid down by Einthoven that $\angle \alpha$ has to be calculated for the greatest wave in the QRS complex is not detailed enough, so that in certain cases one will be in doubt as to which wave is to serve as a basis for the calculation of $\angle \alpha$. As mentioned by Pardee (p. 91), this applies, for instance, to all electrocardiograms in which two waves are equal in size and larger than the other waves no matter whether these two waves occur in different leads (*e. g.*, $R_I = S_{III}$) or in the same lead (*e. g.*, $R_{II} = S_{II}$). As is evident from the preceding, the difficulties are greater because the exact determination of $\angle \alpha$ requires the knowledge of two simultaneous deflections in at least two derivations. For, as demonstrated already by Einthoven, two corresponding waves (*e. g.*, $R_I - S_{III}$ and $S_I - R_{III}$) are not always synchronous, so that it is not enough merely to measure the size of these two waves. Thus, for instance, in 12 electrocardiograms with all three derivations taken simultaneously and showing right axis deviation according to the new criteria given below, I found that the apex of R_{III} in 1 case appeared 0.025 sec. before the apex of S_I , in 2 cases 0.02 sec., in 4 cases 0.015, in 2 cases 0.01, and in 2 cases 0.005 sec. before the apex of S_I ; only in one case was the apex of R_{III} precisely synchronous

with the apex of S_I . Among 47 electrocardiograms with left axis deviation, in 2 cases the apex of R_I preceded that of S_{III} by 0.02 sec., in 8 cases by 0.01 sec., and in 9 cases by 0.005 sec., while the apices of R_I and S_{III} were synchronous in 28 cases. After the introduction of the modern amplifiers built for simultaneous tracing in all three leads, however, the requirement concerning knowledge of the size of synchronous deflections in at least two leads does not involve such great difficulties as previously when particular methods had to be employed in order to meet this requirement — as, for instance simultaneous registration of the heart sounds (Fahr), or the method given by Lewis^{a)} involving a shift in the mutual relation of the three leads till Einthoven's law (Lead II — Lead III = Lead I) is complied with for the entire QRS complex.

But the overcoming of the technical difficulties mentioned does not remedy another shortcoming which in my opinion detracts essentially from the significance of an exact determination of the electric axis and shows that the value obtained for $\angle \alpha$ cannot be taken as a measure for the degree of the axis deviation. In most electrocardiograms with right axis deviation R_{III} will be the largest wave. As the apex of R_{III} in a few cases falls just on the transition between R_I and S_I , and in many cases just in the beginning of S_I — that is corresponding to a small negative deflection in Lead I — $\angle \alpha$ will in such cases be $+ 90^\circ$ or merely a little over 90° and be independent of the size of S_I . If, on the other hand, S_I is the largest wave, the values for $\angle \alpha$ will be disproportionately great, as the apex of S_I often corresponds to a comparatively small positive deflection in Lead III. Corresponding, though less pronounced, features are seen in left axis deviation. As far as that goes, it would be preferable to adopt the procedure often employed in the clinic, namely, to disregard the demonstrated asynchronicity between the deflections in Lead I and Lead III and simply calculate $\angle \alpha$ on the basis of the respective values for $S_I - R_{III}$ and $R_I - S_{III}$. For it is easy in a drawing to establish that no matter whether the apex of S_I falls a little before or a little after the apex of R_{III} , $\angle \alpha$ for $S_I - R_{III}$ will always fall between $\angle \alpha$ for S_I and the synchronous deflection in Lead III and $\angle \alpha$ for R_{III} and the synchronous deflection in Lead I. The same applies to $\angle \alpha$ for $R_I - S_{III}$. Hence the method is not unserviceable clinically, but it is arbitrary, the importance being attached to $\angle \alpha$ for a vector (or resultant) without

particular characteristics even though it appears in the vector cardiogram corresponding to the electrocardiogram.

In the daily work, most often, no determination is made of $\angle \alpha$, various simple rules being employed instead to decide whether or not a given electrocardiogram shows axis deviation. These rules are supposed to have been formulated so that the electric axis (that is, the «arbitrary» electric axis) falls outside the normal range if the rule is observed. Of these rules, the most well-known says there is right axis deviation when the largest waves in Lead I and Lead III face each other, left axis deviation when they turn away from each other. If this rule is observed literally it comes very near covering the cases which, according to my criteria, show right axis deviation. Often, however, electrocardiograms in which S_I , although distinct, is smaller than R_I , are seen to be designated as showing right axis deviation; and the same applies even sometimes to electrocardiograms showing no S_I at all but a low R_I and a high R_{III} . To speak of right axis deviation in such cases is entirely misleading. As to left axis deviation, on the other hand, this rule is quite insufficient. If S_{III} is smaller than one-half of R_I , $\angle \alpha$ will have a value between 0° and $+30^\circ$ and hence it has to be characterized as normal even though S_{III} be greater than R_{III} .

Pardee recommends for clinical purposes merely to decide whether the electric axis falls within the ranges from $+90^\circ$ to $+30^\circ$ (normal axis), from $+30^\circ$ to -30° (slight left axis deviation), from -30° to -90° (pronounced left axis deviation), from $+90^\circ$ to $+150^\circ$ (slight right axis deviation), and from 150° to $+210^\circ$ (marked right axis deviation). The principle for the method has been given by Einthoven. The axis determination can be made rapidly on the basis of the directions of the largest deflection in each of the three extremity leads (see Pardee p. 95—96). Two objections may be raised to this method: In the first place, as the largest deflections in the three leads are not synchronous, the axis determined after this method too will be an «arbitrary» electric axis; secondly, it is unfortunate to designate axis positions from $+30^\circ$ to 0° as left axis deviation because, as mentioned already, the normal range extends from 90° to 0° .

In «Nomenclature and Criteria for Diagnosis of Disease of the Heart» (4' ed. 1939, p. 134), a method is given which to me does not seem expedient and will not be mentioned further here.

In summing up the mentioned methods, which are all based on the determination of $\angle \alpha$ for the electric axis, the following may be said: When the requirement of synchronicity is insisted upon, determination of $\angle \alpha$ for the largest deflection in the electrocardiogram is difficult, and owing to the circumstances demonstrated on p. 317, it is not very suitable for practical purposes. The other methods in which the requirement of synchronicity is relinquished are »arbitrary», leading to determination of $\angle \alpha$ for a vector without particular characteristics. Some of the methods give results that are not in keeping with our present knowledge about the normal range of variation for the electric axis.

Fundamentally different from the mentioned methods are those methods in which the decision of presence or absence of ventricular preponderance in the electrocardiogram depends on the size of certain indices. Such a method was first employed by Lewis^{b)} in his work on the mutual weight relation of the ventricles. Lewis employed the formula $(R_I - S_I) + (S_{III} - R_{III}) = \text{Index}$. He failed, however, to state which index values are normal, or which indicate ventricular preponderance.

Here and in the following, the term »ventricular preponderance» is employed intentionally for the mentioned electrocardiographic changes, because, in the cited works it was assumed that these changes — at any rate when they are pronounced — indicate a relative hypertrophy of one of the ventricles. With the increasing realization of the fact that also axial and conductive changes in the heart are of great significance to the appearance of the electrocardiographic changes mentioned, right and left axis deviation seems now preferable as designation for these phenomena.

White & Bock modified Lewis' formula to $(U_I + D_{III}) - (D_I + U_{III}) = \text{Index}$, in which U and D signify the greatest positive and negative deflections in the respective leads. After examination of about 1200 electrocardiograms, White & Bock state that indices from +20 to +30 and from -15 to -18 usually mean respectively left and right ventricular preponderance and that indices over +30 and under -18 always signify ventricular preponderance. Subsequently White & Burwell set the limit for right ventricular preponderance at -10. Various objections may be raised to White & Bock's formula. In the first place, the index may have the same value for electrocardiograms of widely different appearance — nay,

even the same value for electrocardiograms which, according to the criteria otherwise employed, show axis deviation and for electrocardiograms showing no axis deviation. In an electrocardiogram with $R_I = 10$, $S_I = 0$, $R_{III} = 0$ and $S_{III} = 10$, the index is $+20$, and if R_I and S_{III} are synchronous, $\angle \alpha$ for these waves is -30° (that is, left axis deviation). In an electrocardiogram with $R_I = 20$, $S_I = 0$, $R_{III} = 2$ and $S_{III} = 2$, the index is likewise $+20$, but here $\angle \alpha$ for $R_I - S_{III}$ is $+25^\circ$, and hence it will not be designated as left axis deviation. Furthermore, it will be noticed that large deflections are required if the index is to reach the values set up by White & Bock as limits for ventricular preponderance. Experience shows that in electrocardiograms with ventricular preponderance the deflections are often large but this is far from being an absolute rule. In materials reported by Lewis, by Cotton and by Hermann & Wilson comprising hearts that were dissected in a special manner, a total of 30 specimens showed an abnormal relative increase in the weight of one of the ventricles. Only in 2 out of 18 cases with preponderance of the left ventricle did White & Bock's index exceed $+20$; and only in 2 out of 12 cases with preponderance of the right ventricle was the index more negative than -10 .

In order to evade the latter objection to White & Bock's formula, Schlomka has modified it to

$$\text{Index} = \frac{(O_I - U_I) - (O_{III} - U_{III})}{(O + U)_{\max.}},$$

in which O and U respectively signify the largest positive and negative deflections in the leads concerned, and in which $(O + U)_{\max.}$ gives the numerical sum of the positive and negative deflections in the lead where the sum is greatest. Positive indices signify that the electrocardiogram in question is of relative (index $0 - +1$) or absolute (index $+1 - +2$) left type, while negative indices mean that the electrocardiogram is of relative (index $0 - -1$) or absolute (index $-1 - -2$) right type. But the zero point does not represent electrocardiograms of the same appearance or with the same value for Einthoven's $\angle \alpha$, as is evident from the following examples. In these examples, $\angle \alpha$ is calculated after the formula

$\text{tg } \alpha = \frac{2e_3 + c}{e_1 \sqrt{3}}$, on the presupposition that the greatest deflections in Leads I and III respectively are synchronous.

$$\text{Index} = \frac{(8-2)-(8-2)}{10} = 0. < \alpha = +60^\circ$$

$$\text{Index} = \frac{(12-4)-(8-0)}{16} = 0. < \alpha = +53^\circ$$

$$\text{Index} = \frac{(2-1)-(0-8)}{12} = 0. < \alpha = -124^\circ$$

Also the next two examples illustrate that the same index value may correspond to different values for $< \alpha$. In the first example, the electrocardiogram with an index of +1 shows no left axis deviation, while in the second electrocardiogram with the same index value there is a left axis deviation.

$$\text{Index} = \frac{(17-1)-(3-5)}{18} = +1. < \alpha = +13^\circ.$$

$$\text{Index} = \frac{(14-4)-(3-11)}{18} = +1. < \alpha = -18^\circ.$$

So Schlomka's indices are not definitive either — at any rate not if the values for $< \alpha$ are employed for comparison. Hence the method has to be characterised as unsuitable, or it may be claimed to give an entirely new solution of the axis deviation problem that is more valuable than the conception of this problem originating from Einthoven. But the latter is rather improbable. Einthoven's conception is unquestionably related to the electrical conditions in the heart whereas Schlomka's method is of rather speculative nature.

A fourth formula has been given by Benedetti, as follows:

$$\text{Index} = \frac{R_I}{R_I + S_I} + \frac{S_{III}}{R_{III} + S_{III}}$$

As Benedetti's original paper has not been accessible to me, I shall refrain on commenting on it.

For a decision on the question about axis deviation, the methods based on the calculation of certain indices are not very serviceable. The given formulas are not definitive, and the results obtained in this way have no fixed relation to the value of $< \alpha$ for the electric axis.

Through my efforts to find a clinically suitable definition of right and left axis deviations I have arrived at a new conception of this question.

Einthoven's definition of axis deviation attaches importance only to the direction of the manifest potential corresponding to a

single point in the QRS complex, *i. e.*, at a given moment during the tracing of the QRS complex. According to our present conception of the electrical conditions in the heart, in axis deviation a majority of the dipoles prevailing in the heart at a given moment will be orientated in an abnormal direction, so that the resultant becomes the direction of the electric axis. With a view to the definition of axis deviation it makes no difference whether this preponderance of abnormally directed dipoles is brought about by a relative hypertrophy of certain parts of the myocardium, by disturbances of the conductivity or by rotation of the heart. At present, it will have to be left for clinical electrocardiography to find the means of deciding which of these three causes is present in each individual case. In axis deviation, however, the electric axis is not the only vector with an abnormal direction; at any rate several of the nearest vectors are bound to have an abnormal direction. It will be possible, therefore, to base the definition of axis deviation also on the direction of several of the vectors corresponding to the QRS complex or of the average direction of the total vectors. To me it seems that an axis defined in this way will be more likely to demonstrate abnormalities in the electrocardiogram than the axis defined by Einthoven.

Considering the vector cardiograms for the QRS complex in a number of electrocardiograms with unquestionable left axis deviation, it will soon be noticed that the vector cardiogram in such cases has a characteristic location. As mentioned previously by Schellong, the greater part of the vector cardiogram will fall in quadrant IV (see Fig. 2) as the majority of vectors fall in this quadrant; and, in turn, this means that the greater part of the area circumscribed by the vector cardiogram will lie in quadrant IV. So the following definition of left axis deviation seems acceptable: *The electrocardiogram is said to show left axis deviation when the vector cardiogram corresponding to the QRS complex is located so that the greater part of the area circumscribed by the vector cardiogram is situated in quadrant IV.* Correspondingly, in electrocardiograms with unquestionable right axis deviation the greater part of the vector cardiogram for the QRS complexes will fall in quadrant II (see Fig. 2), so that the definition of right axis deviation will be: *The electrocardiogram is said to show right axis deviation when the vector cardiogram corresponding to the QRS complex is located so*

that the greater part of the area circumscribed by the vector cardiogram is situated in quadrant II.¹

Like all the previous definitions of axis deviation, those given here are arbitrary, but they have unquestionably a relation to the electrical conditions in the heart, even though, as emphasized strongly by Fröhlich, both the electric axis and the vector cardiogram are to be looked upon merely as physical adjuvants, the relation of which to the electrical conditions in the heart is uncertain. Nor is it possible at present to decide whether the new definitions theoretically be preferable to Einthoven's definition, but

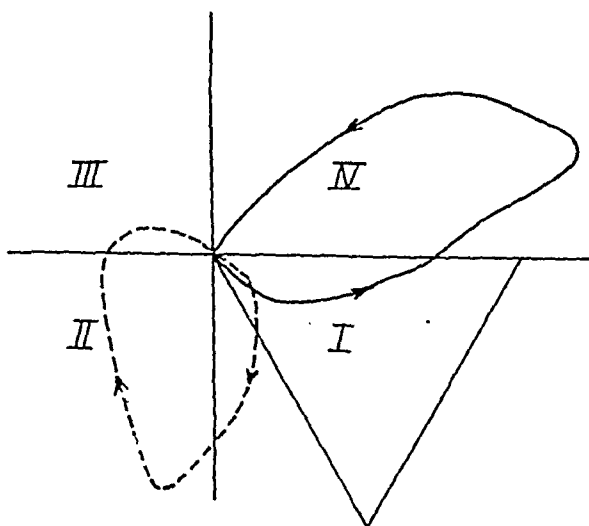


Fig. 2. Vector cardiograms for the QRS complexes in an electrocardiogram with left axis deviation (full-line curve) and in an electrocardiogram with right axis deviation (stippled curve).

as will be evident from the following, they offer a great advantage of entirely practical nature. For with their employment we avoid all the dubious questions associated with the decision as to which QRS vector is to be designated as the electric axis, we also avoid the difficulties connected with the determination of $\angle \alpha$ for this vector.

¹ In the above definitions of axis deviation no regard is paid to how long the individual vectors are present in the vector cardiogram or, in other words, to the varying density of the vectors in the various parts of the vector cardiogram. This is contrary to the methods given by Wilson, McLeod, Barker & Johnston for determination of a mean axis. But, the method given by these authors requires planimetry of the electrocardiograms taken in derivations from the extremities, and this will render the practical employment difficult. Whether the method of Wilson et alien. implies any practical advantages to the following simple procedure may be settled only by further investigation. Studies of this kind have now been commenced in this department by Dr. Nordby.

In order to make the above definitions of right and left axis deviation serviceable in practice, it is necessary to set up some simple rules concerning which electrocardiograms will have vector cardiograms meeting the stipulated requirements. As the conditions are more easily surveyable in right axis deviation, we will consider this first.

When the size and direction of the synchronous deflections in Leads I and III are known, the vector cardiogram can be constructed by plotting along the lines of two acute angles at 60° the deflections of the right size and direction, which may be seen from Fig. 3. At the end-points of the deflections, perpendiculars are

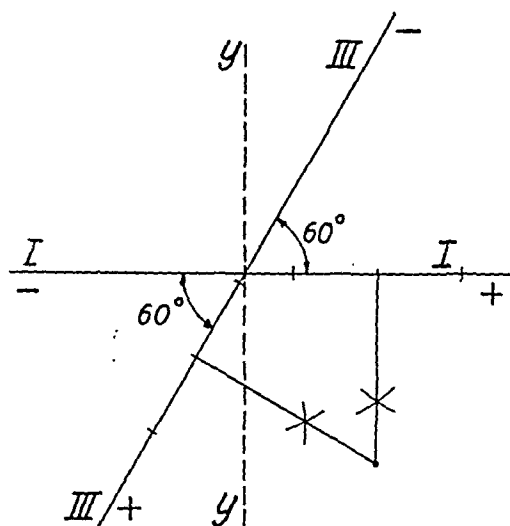


Fig. 3. Construction of the vector cardiogram (see the text).

raised on Leads I and III respectively; the point of intersection for these perpendiculars will be the wanted point of the vector cardiogram. All deflections in Leads I and III may be looked upon as coordinate pairs for a curve (the vector cardiogram) in a skew coordinate system with the abscissa axis I—I, and the ordinate axis III—III. Now the task is to find which conditions the coordinate pairs have to meet if the greater part of the area circumscribed by the curve determined by the coordinate pairs is to be located to the left (the left hand side of the reader) of the perpendicular Y—Y through the apex of the angles. This can be reduced to an analysis of the conditions which the coordinate pairs have to meet if the greater part of the area circumscribed by the curve de-

terminated by the same coordinate pairs in the usual rectangular coordinate system is to be situated to the left of the ordinate axis.

The proof of this is evident from Fig. 4, in which the full-line curve shows a vector cardiogram in the skew coordinate system (axes I—I and III—III). In the rectangular coordinate system (axes X—X and Y—Y) the same curve will have the appearance of the stippled curve. Of the area circumscribed by the first curve a narrow strip is cut out. That part of the strip which is situated to

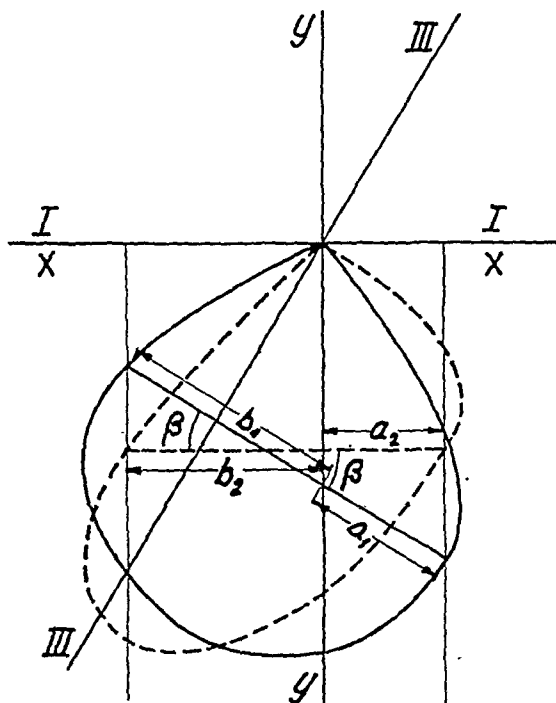


Fig. 4. Vector cardiogram in the skew coordinate system with axes I—I and III—III (full line) and the same vector cardiogram in the rectangular coordinate system with axes X—X and Y—Y (stippled line).

the right of Y—Y has size a_1 , while the part to the left of Y—Y has size b_1 . In the rectangular coordinate system, the coordinate pair which determine this strip will demarkate a strip of an area consisting of two corresponding parts, a_2 and b_2 . As $\angle \beta$ is 30° , we have

$$a_2 = a_1 \cdot \cos \beta \text{ and } b_2 = b_1 \cdot \cos \beta, \text{ which by division give } \frac{a_2}{b_2} = \frac{a_1}{b_1},$$

and this is what had to be proved.

But, owing to the great variability of the electrocardiogram and thus the vector cardiogram too, it will hardly be practicable

even in a rectangular coordinate system to treat the question in an entirely mathematical way. By means of schematic examples, however, it is possible to arrive at an estimate of the conditions that have to be fulfilled by the coordinate pairs, *i. e.*, the deflections in Leads I and III — something that could not be carried through properly in the skew coordinate system.

In the schematic electrocardiogram presented in Fig. 5, the S wave in Lead I is a displaced reflection of the R wave in the same Lead, and the apex of the R wave in Lead III falls just on the transition between the R and S waves in Lead I. The vector cardiogram for such an electrocardiogram will circumscribe equal areas on the two sides of the Y axis. If, on the other hand, S_I is unchanged in size, but of a little longer duration than R_I , or if

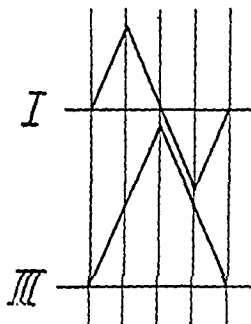
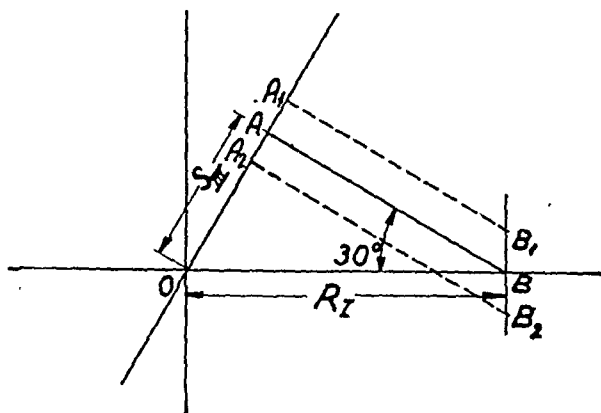


Fig. 5. Schematic QRS complexes in Leads I and III (see the text).

S_I with the same duration is a little greater than R_I , the area to the left of the Y axis will be greater than the area to the right of this axis, provided there is no change in Lead III. The same holds true if Lead I remains as shown in Fig. 5, while the apex of R_{III} appears a little later, that is, corresponding to a point of the S wave in Lead I.

From a number of successive patients whose electrocardiograms were taken simultaneously in all three leads, I therefore have picked out those electrocardiograms which in Lead I showed an S wave which in size and duration exceeded the R wave in the same lead. Altogether 12 electrocardiograms presented this property, and for these records I have constructed the vector cardiograms in the way outlined above. In all 12 cases, the greater part of the area circumscribed by the vector cardiogram lay to the left of the Y axis. In addition, I have examined the vector cardiogram for some

So the electrocardiographic criterion of *right axis deviation* is that the *S wave in Lead I must exceed the R wave in the same lead both in size and duration*. This simple rule covers the above definition of right axis deviation based on the vector cardiogram as accurately as may reasonably be demanded. The location of the R wave in Lead III need not be stipulated precisely, as experience shows that when Lead I fulfills the given criterion, the apex of



this wave will always be in keeping with a point of the S wave in Lead I or, at the earliest, on the transition between the R and the S waves in Lead I.

Left axis deviation: If the S wave in Lead III exceeds the R wave in the same lead in size as well as in duration, the greater part of the area circumscribed by the vector cardiogram will fall above a line perpendicular on Lead III through the zero point, that is, a line with a direction of $+30^\circ$ (cf. right axis deviation). This is brought about in part by the fact that the apex of R_I in such electrocardiograms (see above) most often will be synchronous with the apex of S_{III} or barely precede it. After the definition of left axis deviation, however, the greater part of the circumscribed area will have to be situated above the horizontal line representing Lead I. If a point of the vector cardiogram is to fall above the horizontal

line, the negative deflection in Lead III must be greater than one-half of the synchronous (positive) deflection in Lead I. This is evident from the rectangular $\triangle OAB$ in Fig. 6.

Here we find $OA = \sin 30^\circ \cdot OB$, and as $\sin 30^\circ = \frac{1}{2}$, we have $S_{III} = \frac{1}{2} R_I$. If $S_{III} > \frac{1}{2} R_I$, the point B will fall above the horizontal line — for instance, in B_1 —, whereas if $S_{III} < \frac{1}{2} R_I$, it will fall below the horizontal line in B_2 . So the desired rule for the electrocardiogram must include the stipulation that the negative deflection in Lead III for a certain part of the QRS complex must be greater than one-half of the synchronous positive deflections in Lead I. As such a rule was reckoned to be too complicated for clinical use, I thought it might perhaps be sufficient instead to insist that S_{III} must be greater than one-half of R_I . From the aforementioned patient material whose electrocardiograms were taken simultaneously in all three leads, I have picked out all those electrocardiograms in which S_{III} exceeded R_{III} in size and duration and also was larger than $\frac{1}{2} R_I$. Altogether 47 electrocardiograms of this kind were found and I have constructed the vector cardiogram for all of them. In 38 cases, the greater part of the area circumscribed by the vector cardiogram lay above the horizontal line, while in 6 cases the areas on the two sides of this line were practically equal, and in 3 cases the greater part of the circumscribed area lay below the horizontal line. An analysis of the electrocardiograms in the last-mentioned 9 cases showed that in 6 of them — including all the 3 cases in which the greater part of the circumscribed area lay below the horizontal line — R_{III} was rather large, and in 2 of them there was also a rather large second positive wave. Further examination of the quantitative relation between the R waves and the S waves in Lead III in the respective electrocardiograms shows that the requirement for left axis deviation must be: that the S wave in Lead III is at least 3 times larger than the R wave in the same lead. *The empirical rule for left axis deviation is, therefore. The S wave in Lead III must be at least three times larger than the R wave in the same lead, and it must exceed it in duration; in addition, the S wave in Lead III must be at least half as large as the R wave in Lead I. Or, as an S wave which is at least three times as large as the R wave will always exceed the latter in duration too, the rule may be put down simply as follows: The S wave in Lead III must be at least three times as large as the*

R wave in Lead III and also larger than one-half of the R wave in Lead I.

These rules for the axis deviation are not applicable to electrocardiograms of a certain though rare form, namely: electrocardiograms in which the S waves both in Lead I and in Lead III are just as large as the R waves in these leads or even larger. In such cases the vector cardiogram will present a peculiar outline and be situated especially in quadrants I and III.

It will be consistent to look upon all electrocardiograms complying with the given rules as cases of axis deviation — thus, for instance, also electrocardiograms with a large Q_{III} when this Q wave is large enough to meet the requirements stipulated for S_{III} in left axis deviation, besides electrocardiograms showing various forms of bundle branch block. In practice this will not give rise to any difficulty; the two mentioned forms of electrocardiograms (and perhaps others) will merely constitute an easily recognizable subgroup of the axis deviations where the cause of the axis deviation is to be considered established as conductive disturbances.

The definitions and rules given here will allow of a certain estimate of the degree of the axis deviation. For it is obvious that the larger and broader the S waves are in relation to the R waves in the respective leads, the greater will that part be of the area circumscribed by the vector cardiogram which falls outside quadrant I. But the definitions also imply the possibility of a quantitative measure for the degree of the axis deviation. Studies on this question are now being carried out here in the department. Until the results of these studies are available, however, it will be necessary for a numerical determination of the degree of axis deviation to make use of one of the methods given previously for this purpose — preferably determination of Einthoven's $\angle \alpha$ for the electric axis.

Summary.

After a critical review of the methods hitherto employed to decide whether or not a given electrocardiogram shows axis deviation, the following definitions of axis deviation are set up:

The electrocardiogram is said to show right axis deviation when the vector cardiogram corresponding to the QRS complex is situa-

ted so that the greater part of the area circumscribed by the vector cardiogram falls in quadrant II.

The electrocardiogram is said to show left axis deviation when the vector cardiogram corresponding to the QRS complex is situated so that the greater part of the area circumscribed by the vector cardiograms falls in quadrant IV.

These definitions are then shown to be covered by the following simple electrocardiographic rules:

The electrocardiogram shows right axis deviation when the S wave in Lead I in size and duration exceeds the R wave in the same lead.

The electrocardiogram shows left axis deviation when the S wave in Lead III is at least 3 times as large as the R wave in Lead III and also larger than one-half of the R wave in Lead I.

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An anti-reagin in the desensitization of patients with allergic diseases.

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Allergic symptoms are due to the reaction between the allergen and the sessile reagins of the shock organs as lungs, nose, skin and intestines. About the way in which the recovery occurs in desensitization with the allergen, is but little known with certainty. The general opinion is that the desensitization cure causes a recovery by a diminution of the reagin content of the tissues. However, an increase of the circulating reagins can also have a favorable effect by means of the interception of the entered allergen, so that this cannot penetrate into the sessile reagins of the shock organs. Moreover, Cooke and his collaborators (1935) were able to prove the important fact that in desensitization of patients suffering from hay fever, an immune substance develops.

When the serum of an untreated hay fever patient (A serum) is mixed in vitro with pollen extract and then injected into the skin of a normal test person, a reaction occurs within half an hour. Re-injection of allergen in the same place after 24 hours gives no new reaction.

Cooke c.s. was able to demonstrate that this test gives quite another effect when it was performed with the serum of a patient with hay fever who was desensitized to a very high dose (P. serum). This serum, mixed in vitro with allergen during 24 hours after

which it is injected intracutaneously, gives no reaction within half an hour, but reinjection of the allergen after 24 hours in the same skin part now causes a reaction. Cooke ascribed this difference to the appearance of a substance in the blood which was able to inhibit the allergen-reagin reaction and was termed the Reaction Inhibiting Substance (RIS) by him. Cooke, and after him Harley, only demonstrated this phenomenon in patients with hay fever.

Table 1.
Test of Cooke.

Mixtures	Skin reactions	
	After ½ hour.	Injection of pollen-extract after 24 hours.
Serum A + Pollenextract		 
Serum A + Phys. salt sol.		
Serum P + Pollenextract		
Serum P + Phys. salt sol.		

Serum A (ante) = serum before the desensitization.
Serum P (post) = serum after the desensitization.

Anticipating the results of our own investigation, in which we determined the nature of the RIS, in future we will not speak of an inhibiting substance but of an anti-reagin. To get an insight into the importance of the reagins and the inhibiting substance of Cooke, we studied the quantity of sessile and circulating reagins, the

quantity of anti-reagins and the clinical symptoms in mutual connection before, during and after the desensitization cure.

Own investigation.

For the hay fever desensitization we used an extract of *Dactylis glomerata*, standardized according to Noon. This species of pollen was chosen because our patients showed a stronger reaction to it than to 9 other species of grass of frequent occurrence. Moreover this pollen could easily be collected. The desensitization was nearly always forced up to the very large dose of 100,000 units a time.

General reactions were seldom seen. If present, $\frac{1}{2}$ cm³ of sym-patol was temporarily added to the dose of vaccin. From the other allergens 1 % extracts were made from the dry »Lifa« protein with the liquid of Coca. From this dilutions were made 1: 10; 1: 100; 1: 1000 concentrated solutions for the desensitization cure. With the inhalation-allergens, especially hay fever, the nose sensitiveness was determined by spraying solutions of pollen of 1000, 10,000 and 100,000 units upon the concha inferior. If the reaction was positive, swelling, sneezing and secretion of fluid occurred. The technic and the results of this nose-threshold reaction will be published separately in due time.

Sessile reagins.

For the determination of the tissue-sensitiveness we used intracutaneous threshold reactions with extracts of increasing concentrations of which 0.1 cm³ was injected into the skin of the patient. The extract which just gave a reaction after half an hour was considered as the sensitiveness-threshold.

We made these reactions before, during and after the desensitization cure.

Some typical examples may follow here. (Table 2).

Serum reagins.

For the quantitative determination of the serum reagins we used the passive transmission of Prausnitz and Küstner. Dilutions of the serum with physiological salt solutions of 1: 5, 1: 10, 1: 50, 1: 100 were injected into the skin of normal test persons, after 24 hours an excess of allergen was injected accurately in the same canal. A

positive reaction with a strongly diluted serum points to a large quantity of reagins. Table 3 shows at which dilutions the A serum and the P serum of a certain patient gave still a reaction. It appeared that the A sera had to be of a stronger concentration, that is to say appeared to contain less reagins than the P sera.

Table 2 a.
Intracutaneous threshold reactions in patients suffering from hay fever.

Patient	Date of determinations	Reaction threshold in Noon units	Maximal dosage of Noon units per injection
H. K.	21— 1—1941	1	0
	15— 4—1941	10	8000
	23— 9—1941	100	100000
J. B.	7— 1—1941	10	0
	8— 4—1941	100	20000
	30— 9—1941	1000	100000
J. v. d. W...	25— 2—1941	10	0
	11— 4—1941	100	20000
	16— 9—1941	1000	100000
A. G.	21— 4—1941	10	0
	5— 3—1941	1	2000
	7— 5—1941	100	30000
	30— 9—1941	1000	100000
K. G.	25— 2—1941	100	0
	11— 4—1941	10	2000
	30— 9—1941	1000	100000
L. R.	28— 1—1941	1	0
	11— 2—1941	1	2000
	11— 4—1941	100	8000
	23— 9—1941	1000	100000
S. B.	14— 2—1941	10	0
	11— 4—1941	1000	8000
	23— 9—1941	1000	30000
A. P.	8— 8—1941	10	0
	24— 9—1941	1	2000
	10—11—1941	100	4000
	9— 1—1942	1000	40000

Table 2 b.
Tobacco-hypersensitiveness.

Patients	Dates of determinations	Intracutaneous thresholdreactions	Maximal quantity injected per time
K. G.	25—2—1941	0.01 % extract	
	15—3—1941	0.002 % »	1 cm ³ 1% extract
	25—4—1941	0.1 % »	1 cm ³ 1% »
	30—9—1941	1 % »	1 cm ³ 1% »
L. R.	28—1—1941	0.001 % extract	
	15—2—1942	0.0001% »	1 cm ³ 1% extract
	11—4—1941	0.001 % »	1 cm ³ 1% »
	15—7—1941	0.1 % »	1 cm ³ 1% »
	23—9—1941	1 % »	1 cm ³ 1% »

Table 2 c.
Feather-hypersensitiveness.

Patients	Dates of determinations	Intracutaneous thresholdreactions	Maximal quantity injected per time
B. L.	3—10—1941	0.1 % extract	
	17—10—1941	0.01 % »	2 cm ³ 1% extract
	9— 1—1942	1 % »	2 cm ³ 1% »
A. W.	7—10—1941	0.1 % extract	
	9— 1—1942	1 % »	1 cm ³ 1% extract

Table 2 d.
Beans-hypersensitiveness.

Patients	Dates of determinations	Intracutaneous thresholdreactions	Maximal quantity injected per time
G. G.	30— 9—1941	0.1 % extract	
	14—10—1941	0.01 % »	2 cm ³ 1% extract
	3—12—1941	0.1 % »	2 cm ³ 1% »
	24— 1—1942	1 % »	2 cm ³ 1% »

Table 3a.

Quantity of reagins in the hay fever-serum A and P.

Serum	Diluted with phys. salt	Tp: W. S: G. S.	Tp: J. G. S: A. G.	Tp: T. N. S: A. G.	Tp: Gr. S: v. d. W.	Tp: d. M. S: v. d. W.	Tp: d. W. S: H. K.	Tp: W. J. S: H. K.	Tp: v. D. S: H. K.	Tp: K. L. S: K. G.	Tp: W. S: K. G.	Tp: W. B. S: J. B.	Tp: J. G. S: J. B.	Tp: H. R. S: J. B.
A	1-5	+	+	+	+	+	+	+	+	+	+	+	+	±
A	1-10	+	+	+	+	+	+	+	+	+	+	+	+	±
A	1-50	+	+	+	+	+	+	+	+	+	+	+	+	±
A	1-100	+	+	+	+	+	+	+	+	+	+	+	+	±
A	1-200	+	+	+	+	+	+	+	+	+	+	+	+	±
A	1-300	+	+	+	+	+	+	+	+	+	+	+	+	±
P	1-5	+	+	+	+	+	+	+	+	+	+	+	+	+
P	1-10	+	+	+	+	+	+	+	+	+	+	+	+	+
P	1-50	+	+	+	+	+	+	+	+	+	+	+	+	+
P	1-100	+	+	+	+	+	+	+	+	+	+	+	+	+
P	1-200	+	+	+	+	+	+	+	+	+	+	+	+	+
P	1-300	+	+	+	+	+	+	+	+	+	+	+	+	+

0.1 cm³ of these serum-dilutions were injected intracutaneously in the back of normal persons, after 24 hours reinjection was done in the same place with a 0.1 cm³ pollen solution containing 4000 Noon units per cm³

Tp = test person. S = serum from patient

Comparison of the reactions of the serum A- and serum P-dilutions, shows that after treatment the quantity of serum-reagins has also increased in patients suffering from hay fever.

Table 3b.

Quantity of reagins in serum A and Serum P in house-dust-hypersensitiveness.

Serum	Phys. salt dilut.	Tp: A. H. S: J. B.	Tp: T. R. S: J. B.	Tp: R. O. S: A. G.	Tp: S. A. S: A. G.	Tp: A. d. B. S: H. t. B.	Tp: J. C. S: O. v. V.	Tp: M. B. S: H. E.	Tp: F. K. S: H. E.	Tp: A. D. S: H. E.	Tp: T. E. S: W. G.	Tp: W. V. S: N. H.
A	1-0	+	+	+	+	+	+	+	+	+	±	+
A	1-5	+	+	+	+	±	±	+	±	±	0	+
A	1-10	0	0	0	0	0	0	0	0	0	0	0
A	1-50											
A	1-100											
A	1-200											
A	1-300											
P	1-0	+	+	+	+	+	+	+	+	+	+	+
P	1-5	+	+	+	+	+	+	+	+	+	+	+
P	1-10	+	+	+	+	+	+	+	+	+	±	+
P	1-50	+	+	+	+	+	+	+	+	+	0	+
P	1-100	0	0	±	±	0	0	0	±	±	0	0
P	1-200											
P	1-300											

As the reactions of the P-sera are stronger than the same dilutions of the A-sera, and where the A-dilutions remain quiet, whereas the same P-dilutions gave still a marked reaction, the quantity of reagins in the P-sera must have increased considerably.

Table 3 c, d, e, and f.

Cont.

+ Serum	Phys. salt solut.	Tp: K. M. Ser: K. G.	Tp: C. N. Ser: K. G.	Tp: J. S. Ser: K. G.	Tp: S. K. Ser: L. R.	Tp: R. W. Ser: L. R.	Tp: H. K. Ser: L. R.	Hypersensitiveness to tobacco.
A	1—5	+	±	+	+	0	+	
A	1—10	0	0	±	0	0	±	
A	1—50			0		0	0	
A	1—100							
A	1—200							
A	1—300							
P	1—5	++	++	++	+++	0	++	
P	1—10	+	+	+	++	0	++	
P	1—50	0	±	0	±	0	+	
P	1—100		0		0		0	
P	1—200						0	
P	1—300							

Comparison of the results of the skin threshold reactions and the passive transmission learned that there is an important contrast. At the outset of the desensitization cure the skin sensitiveness has increased; at a higher dosage the skin sensitiveness decreases considerably (table 2). This decrease, however, is not due to a diminution of the reagins but to the development of the anti-reagin. In the last case, just as in the test of Cooke, the inhibiting substance prevents the reaction of allergen and reagins. The anti-reagin, however, has the remarkable property (experimentally ascertained by us) to disappear from the skin so that the reagin can again react undisturbed with the allergen. So it was only possible to determine an increase of the amount of reagins during the desensitization cure by means of the passive transmission. This increase develops soon, and before the anti-reagins can be demonstrated. So a recovery by desensitization must not be attributed to a diminution of the reagin content. Housedust forms an exception in that the reagin increase was very marked but that the presence of anti-reagins could not be demonstrated.

Demonstration of anti-reagins in other allergic affections.

When a favorable clinical result was obtained, serum was taken from the patient (P serum). This serum was compared with the serum of the patient before the treatment (A serum) by means of the

test of Cooke. We could demonstrate the presence of the anti-reagin not only in patients with hay fever but also in patients suffering from asthma, rhinitis vasomotoria and dyspepsia by a hypersensitiveness to tobacco, feathers, toilet powder, beans and flour. So here we are not concerned with a specific symptom of hay fever, but with a phenomenon which probably can occur in each desensitization and in all allergies. Our patients with a hypersensitiveness to housedust formed an exception. However, the quantity of housedust-allergen which was administered is too small to cause an anti-reagin, just as in pollen desensitization under 25,000 units. When the injected quantity of allergen for the housedust and pollen desensitization is expressed in multiples of the quantity of allergen with which a skin reaction is still just obtained (0.1 % housedust and 10 units pollen), a dose of housedust of 1 cm³ 5 % corresponds in fact with 500 units of pollen extract. The use of a larger dose of housedust is impossible from a technical point of view as long as we cannot isolate this allergen in a purer condition. This is the reason why a desensitization with a demonstrable anti-reagin should perhaps be attainable only by very frequent injections. Up to now, however, we did not succeed, even not after 60 injections of 5 % extract, but the clinical results with housedust desensitization in asthma and rhinitis vasomotoria are very satisfactory.

Quantitative determination of the anti-reagins: inhibition index.

During the desensitization cure of a number of patients serum was taken at intervals, and also from patients whose cure had been terminated for a long time past. We now examined to which extent these P sera from different phases of the cure were able to inhibit the reaction of a certain quantity of A serum: i. e. if a certain excess of anti-reagin was present. For this purpose we prepared 10 mixtures, namely:

- 9 parts of A serum + 1 part allergen + 1 part P serum.
- 8 parts of A serum + 1 part allergen + 2 parts P serum
- 7 parts of A serum + 1 part allergen + 3 parts P serum
- etc.

From these determinations it appeared that an excess of anti-reagin is present in the serum, which fact is of much clinical importance. It must be well kept in mind that a considerable quantity of anti-reagin must already be present to obtain a non-appearance of the

direct reaction in the test of Cooke, because then nearly all the reagins which are present must be inhibited. The anti-reagin content can be expressed in the number of parts of A serum which are inhibited by a certain number of parts of P serum. When this is expressed in a fraction of which the A serum forms the numerator and the P serum the denominator, this fraction can be termed the *Inhibition Index of the P serum*. When f. i. 6 parts of A serum are inhibited by 3 parts of P serum, the inhibition index is $\frac{6}{3}$. Table 4 gives some examples of it.

With a desensitization to 100,000 units an inhibition index of $\frac{6}{3}$ was usually obtained. A larger inhibition index was never seen.

It appeared that in hay fever desensitization the anti-reagin can be demonstrated only at a dosage of 25,000 units. It also appeared that not only the strength of the dosage but also the duration of the injection, i. e. the total quantity of allergen which is administered, is of importance for the development of the anti-reagins. In bean desensitization for instance the dose was not made larger than 2 cm of 1 %. In the beginning no anti-reagin could be demonstrated with this dose, later the anti-reagin was found to be present.

After termination of the desensitization cure the anti-reagin is demonstrable in the serum during a long time. Six months after the cure only a small decrease could be found. So the test of Cooke is a means to examine for instance if in patients with hay fever, reinjection of the allergen is desirable before the next hay fever season in order to obtain an increase of the anti-reagin.

Preserved as serum at 8° C., the anti-reagin can be kept as well as the reagin itself. Even after one year no diminution of the activity could be found by us with the above described quantitative method.

Specificity.

1. *Does the anti-reagin in the P. serum of one patient inhibit the A serum of another patient with the same allergy?*

To answer this question two mixtures of equal parts of A and P serum were made: one mixture of serum A with serum P of one certain patient, and a mixture of serum A of this patient and serum P of another patient with the same allergy. With these mixtures the test of Cooke was made in the above described way. In 4 cases

Table 4.

Quantitative determination of the anti-reagins.

(s. A = A serum; s. P. = P serum; A. E. = Allerg. extract)

Donor Ser. P.	T. person	Sort of allergy	$\frac{1}{2}$ hour reaction										Max. dosage per time
			s.A 9p. s.P 0p. A.E. 1p.	s.A 8p. s.P 1p. A.E. 1p.	s.A 7p. s.P 2p. A.E. 1p.	s.A 6p. s.P 3p. A.E. 1p.	s.A 5p. s.P 4p. A.E. 1p.	s.A 4p. s.P 5p. A.E. 1p.	s.A 3p. s.P 6p. A.E. 1p.	s.A 2p. s.P 7p. A.E. 1p.	s.A 1p. s.P 8p. A.E. 1p.	s.A 0p. s.P 9p. A.E. 1p.	
V. S.	M. K.	Cosmetic powder (fresh serum)	++	+	±	—	—	—	—	—	—	—	1 cm ³ 1 % solut.
V. S.	J. W.	Cosmetic powder (ser. 4 mths old)	++	+	+	—	—	—	—	—	—	—	
V. S.	F. K.	Cosmetic powder (fresh serum)	++	++	++	+	—	—	—	—	—	—	last injection 4 months ago
d. J.	T. W.	Cosmetic powder	++	++	±	—	—	—	—	—	—	—	1 cm ³ 1 % solut.
K. G.	Mv. I.	Tobacco (fresh serum)	+++	++	+	—	—	—	—	—	—	—	1 cm ³ 1 % solut.
K. G.	S. K.	Tobacco (serum 4 months old)	+++	++	+	—	—	—	—	—	—	—	
L. R.	N. W.	Tobacco	++	++	+	—	—	—	—	—	—	—	1 cm ³ 1 % solut.

of hay fever, 1 case of tobacco- and 1 case of cosmetic powder-hypersensitiveness no difference in inhibiting power of the own P serum and the P serum of the other patient appeared to be present. *So the anti-reagin is not individually specific.* Herewith the possibility for a therapeutic use of the P serum of one patient for another patient is now, at least theoretically, demonstrated.

2. Does the P serum, which is obtained in the desensitization for one certain species of Pollen, inhibit the reaction between another species of pollen and its specific reagin?

The A serum of a patient who was sensitive to Phleum was mixed with the P serum of a patient who was desensitized for Dactylis glomerata. Phleum extract was added to the mixture as allergen. A complete inhibition appeared to occur. So each pollen anti-reagin can probably prevent all pollen reactions in every patient with hay fever. From this the conclusion can be drawn that for desensitization each allied species of pollen can be used, provided the patient reacts positively to this species. This fact is of importance for the therapy of hay fever.

3. Is the anti-reagin for a certain allergen (for instance cosmetic powder) able to inhibit the reactions of an alien allergen (for instance tobacco)?

5 Mixtures were made of which each contained 2 parts of cosmetic powder-A serum and 1 part of cosmetic powder-extract. To 4 mixtures 2 parts of P serum (for each mixture of another allergen, namely of cosmetic powder, tobacco, pollen and beans) were added. We knew that these P sera had a high inhibition index, sufficient to inhibit a same quantity of similar A serum. To the last mixture 2 parts of physiological salt solution were added instead of P serum. In this control mixture there was not a single impediment for the reaction of the allergen with its specific reagin. (table 5)

From these experiments it appears that in this regard the specificity of the anti-reagin is very sharp. So the possibility to make an anti-reagin which prevents all allergic reactions does not exist.

Table 5.
The anti-reagins are allergen-specific.

Serum allergen. mixtures					Reactions on the dorsal skin of the non-allergic test persons after half an hour								
Serum	Sort of hypersensitiveness	Serum	Sort of hypersensitiveness	Sort of allerg. extr.	L. R	J. W.	L. K.	W. R.	H. S.	J. V.	M. W.	A. H.	H. M.
1. A.	cosmetic powder	+	P cosmetic powder	+	cosm. powd.	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
2. A.	cosmetic powder	+	P tobacco	+	cosm. powd.	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
3. A.	cosmetic powder	+	P pollen	+	cosm. powd.	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
4. A.	cosmetic powder	+	P beans	+	cosm. powd.	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
5. A.	cosmetic powder	+	P physiological salt	+	cosm. powd.	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
1. A.	grass pollen	+	P grass pollen	+	grass p.	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
2. A.	grass pollen	+	P cosmetic powder	+	grass p.	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
3. A.	grass pollen	+	P tobacco	+	grass p.	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
4. A.	grass pollen	+	P beans	+	grass p.	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
5. A.	grass pollen	+	P physiological salt	+	grass p.	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
1. A.	tobacco	+	P tobacco	+	tobacco	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
2. A.	tobacco	+	P cosmetic powder	+	tobacco	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
3. A.	tobacco	+	P beans	+	tobacco	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
4. A.	tobacco	+	P grass pollen	+	tobacco	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.
5. A.	tobacco	+	P physiological salt	+	tobacco	pos.	pos.	pos.	pos.	pos.	pos.	pos.	pos.

From these reactions the allergen-specificity of the anti-reagins can distinctly be seen. These are present in the serum P and inhibit only the corresponding serum A (see the numbers 1). The anti-reagins do not inhibit the serum A of the other hypersensitiveness (compare the numbers 2, 3 and 4 with the control-reactions nr 5).

4. *Is it possible to produce an anti-reagin in animals and can this animal anti-reagin inhibit a homologous human A serum?*

If this were possible a new species of allergic immune serum could be prepared. The results of our experiments concerning this matter will be communicated later.

The point of attack of the anti-reagin.

The point of attack of the anti-reagin can be: 1. the cell; 2. the allergen; 3. the reagin.

ad. 1 Injection of a mixture of P serum and allergen, immediately after preparation, into the skin of a normal test person, causes a reaction. Injection 3 hours after preparation causes no reaction (just as in the test of Cooke). So the development of the reaction does not depend on the cells, but on the binding of the inhibiting substance in vitro with the allergen or with the reagin.

ad. 2. If the inhibiting substance made the allergen inactive, this might also give no reaction, even if a great excess of reagins was present as is the case in the skin of a treated hay fever patient. However, injection of P serum with a small quantity of allergen into the skin of a hay fever patient, causes (just as with free allergen) a strong reaction.

ad. 3. The above mentioned experiments make it very probable that the inhibiting substance binds with the reagins. Besides, the determination of the inhibition index made it clear that the anti-reagin binds a fixed quantity of A serum, independent of the quantity of allergen which is administered. So we think it allowed to replace the name inhibiting substance by *anti-reagin*.

So, as far as the-specificity is concerned the anti-reagin corresponds completely with the reagin. However, where the reagin in passive transmission can still be demonstrated in the skin, even after 6 months, the anti-reagin has disappeared from the skin after some hours. To determine this time we injected P serum into the skin of a test person on 12 places and, with intervals of one hour, injected the corresponding allergen into a place. (Table 6.)

It appeared that already after 10 hours the maximal reaction was again obtained in all sorts of allergies. Also the binding of

Table 6.

Serum P.	Do- nor	T. per- son	Reaction with the corresponding allerg. extract after:											
			1 h.	2. h.	3 h.	4 h.	5 h.	6 h.	7 h.	8 h.	9 h.	10 h.	11 h.	12 h.
Hayfever	A. G.	F. K.	—	—	—	—	—	—	±	+	++	+++	+++	+++
Cosm. p.	v. S.	S. K.	—	—	—	—	—	—	—	—	+	++	++	++
Tohaceo	L. R.	J. W.	—	—	—	—	—	—	—	+	++	++	++	++
Feathers	B. L.	S. H.	—	—	—	—	—	—	—	±	++	++	++	++

the anti-reagin with the reagin is loose. Perhaps the anti-reagin is small-molecular which makes a resorption more easy than a large-molecular reagin.

The anti-reagin and the morbid symptoms.

It now is very tempting and obvious to consider the anti-reagin as the serological substrate by which the improvement is effected. Just as in infectious diseases where the anti-toxines neutralize the toxines, in the allergies the anti-reagins could make the reagins inactive by which the resorbed allergen is turned as innocent as in a non-allergic organism. We found that a high dose and a high anti-reagin content gave very good clinical results indeed. On the other hand, however, there is the unmistakable fact that an improvement of the allergic symptoms is also possible without demonstrable anti-reagin, whereas the reagin content of blood and tissues has increased. This is the case in the usual hay fever (4000 units) and house dust desensitization where very satisfying results were obtained. So we have to formulate the paradox that a recovery is possible both with (or by) reagin binding and with (or by) reagin increase. The less favorable results must perhaps be imputed to an inappropriate intermediate dose, in which the reagin increase is compensated by the anti-reagin formation. Perhaps also other unknown factors play a part.

Summary.

In the desensitization of allergic patients an increase both of the circulating and the sessile reagins occurs already with the use of low doses. With high doses an inhibiting substance develops, which was demonstrated by Cooke in hay fever patients. This substance

appeared also to be present in inhalation and food allergies, excepted house dust. The inhibiting substance does not affect the cell or allergen but binds in vitro with the reagin. Therefore the denomination anti-reagin is permitted. As a rule the reagin is present in the serum as an excess and able to bind a certain quantity of reagins which are added. In this way the quantity of anti-reagin can be determined (*inhibition index*). The anti-reagin is not individually specific, so that the serum of a treated patient has also an inhibiting influence upon an untreated patient. The anti-reagin and the reagin are both sort-specific: the anti-reagins for pollen have no inhibiting influence upon a feather- or housedust-allergy. The recovery by desensitization with high doses (pollen above 25000 units a time) must most probably be ascribed to an anti-reagin formation. The favorable results with small doses are perhaps due to a reagin increase.

Résumé.

Lors de la désensibilisation de malades allergiques, les réagines circulantes, de même que celles qui sont combinées, augmentent toujours quand les doses sont basses. Si elles sont élevées, il se forme une substance freinante dont Cooke a démontré la présence chez les malades ayant la fièvre des foin. Cette substance a été trouvée par les auteurs aussi dans les allergies inhalatoires et alimentaires, à l'exception de celles de la poussière des maisons. La substance freinante n'agit pas sur la cellule ou sur l'allergène, mais se combine à la réagine et cela déjà in vitro. Il est donc justifié de parler d'anti-réagine. L'anti-réagine est le plus souvent en surabondance dans le sérum et elle peut combiner une certaine quantité des réagines apportées. On peut déterminer ainsi la quantité d'anti-réagine (index du freinage). L'anti-réagine n'est pas individuellement spécifique, de sorte que le sérum d'un malade traité peut agir aussi sur un malade non-traité. De même que la réagine, d'anti-réagine est spécifique quant à la sorte; les anti-réagines du pollen n'exercent donc pas d'action freinante sur une allergie des plumes ou de poussière des maisons. La guérison qui se produit lors de la désensibilisation par des doses élevées (pollen au dessus de 25000 U. par fois) est très vraisemblablement le résultat d'une formation d'anti-

réagine. Par contre, les résultats favorables obtenus par de moindre doses sont peut-être justement la suite d'une augmentation de réagine.

Zusammenfassung.

Bei der Desensibilisation allergischer Patienten vermehrten sich immer bei niedrigen Dosen sowohl die zirkulierenden als die sessilen Reaginen. Bei hohen Dosen bildet sich eine hemmende Substanz, die Cooke bei Heufieberpatienten nachweisen konnte. Auch bei anderen Inhalations- und Nahrungsallergien, mit Ausnahme von Hausstaub, war dieser Stoff vorhanden. Die hemmende Substanz wirkt nicht auf die Zelle oder auf das Allergen sondern bindet sich an das Reagin, schon in vitro. Die Bezeichnung Anti-Reagin ist daher zulässig. Das Anti-Reagin ist häufig im Übermass im Serum vorhanden und ist imstande, eine bestimmte Menge hinzugefügter Reagine zu binden. Auf diese Weise ist die Menge Anti-Reagin zu bestimmen (Hemmungsindex). Das Anti-Reagin ist nicht individuell spezifisch, sodass das Serum eines behandelten Patienten, auch bei einem unbehandelten Patienten, hemmend wirkt. Das Anti-Reagin ist, ebenso wie das Reagin, wohl artspezifisch, sodass die Anti-Reagine für Pollen keine hemmende Wirkung auf eine Feder- oder Hausstauballergie ausüben. Die Heilung bei Desensibilisierung mit hohen Dosen (Pollen über 25000 E. jedesmal) ist höchstwahrscheinlich einer Anti-Reaginbildung zuzuschreiben. Die günstigen Resultate bei geringer Dosierung sind dagegen vielleicht gerade die Folge von Reaginvermehrung.

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Ein Beitrag zur Frage nach der Pathogenese, Ätiologie und Therapie der eosinophilen Lungeninfiltrate.

Von

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(Bei der Redaktion am 27. April 1943 eingangen).

Kartagener, 1942, v. Meyenburg, 1942, 1943 und Staehelin, 1942, haben die pathologische Anatomie, die Pathogenese und die Klinik der zuerst von Löffler erkannten eosinophilen Lungeninfiltrate geschildert.

Die grundlegende Arbeit v. Meyenburgs, in der er erstmalig Sektionsfälle von Lungeninfiltraten eosinophilen Typs vorlegt, verzeichnet in zwei Fällen Bronchopneumonien mit zugehöriger Bronchitis, was den Autor vermuten lässt, dass es sich um bronchogene Entstehung handle. In den beiden anderen Fällen bestanden keine Zeichen einer Bronchitis oder Bronchiolitis; das Bild sprach hier für Herdpneumonien hämatogenen Ursprungs. Diese Auffassung wurde durch den Umstand bestärkt, dass sich gerade in diesen beiden Fällen auch Leberinfiltrate mit reichlichen eosinophilen Leukozyten fanden. Das Vorkommen eosinophiler Infiltrate an anderen Stellen als in den Lungen wird auch durch eine kasuistische Mitteilung belegt: bei einem jungen Mann mit Verdacht auf Epididymis- und Lungentuberkulose fand man eosinophile Infiltrate in der Epididymis und ein flüchtiges Infiltrat in der Lunge nebst Bluteosinophilie.

Der Fall 1 meines im folgenden vorgelegten Materials weist nicht nur Bluteosinophilie auf, sondern daneben mit grosser Wahrscheinlichkeit ähnliche Reaktionen seitens mehrerer anderer Gewebe und Organe.

v. Meyenburg fasst die bisherigen Auseinandersetzungen über die Ätiologie der eosinophilen Lungeninfiltrate übersichtlich zusammen. Sein eigenes Material untersucht er sorgfältig im Hinblick auf die Ätiologie, im wesentlichen mit negativem Ergebnis. In einem Falle waren jedoch Diplokokken in den Entzündungsherden zu finden. Er erwähnt auch, dass Maas bei einem flüchtigen Lungeninfiltrat Diplokokken mit und ohne Kapsel gefunden hat.

In Fall 1 und 2 unseres Materials sind bei wiederholten Untersuchungen Pneumokokken bestimmten Typs nachgewiesen worden. Wir haben deshalb — soweit ich sehen kann, als erste — die eosinophilen Lungeninfiltrate mit Chemotherapie (Sulfathiazol) zu behandeln versucht, und zwar mit augenscheinlich gutem Erfolg.

v. M. folgert, dass das eosinophile Lungeninfiltrat eine entzündliche allergische Reaktion der Lunge gegenüber verschiedenen Antigenen ist, die auf verschiedenen Wegen eindringen können; sowohl er als andere (z. B. Kartagener) haben darauf hingewiesen, dass für das Vorliegen einer Allergie Fälle sprechen, die auch sonst Überempfindlichkeitssymptome zeigen, wie Urtikaria, Quinckesches Ödem, Rhinitis vasomotoria, Asthma bronchiale

Fall 2 zeigt, dass die Reaktionsweise des Organismus längere Zeit bestehen oder sich wiederholen kann, so dass eosinophile Lungeninfiltrate auch nach einem 3jährigen Intervall wieder auftreten können.

Die Fälle 1, 3 und 4 weisen rheumatische Gelenksymptome auf, eine allergische Manifestation, die bisher bei Fällen der Löfflerschen Krankheit noch nicht beobachtet worden zu sein scheint.

Die vieldebattierten rheumatischen Pneumonien (siehe z. B. Edström, 1937, Gamna, 1940) treten bei rheumatischem Fieber auf, besonders in vorgeschrittenen Stadien. Die besagten Veränderungen sind nicht von der Art, dass man sie mit eosinophilen Lungeninfiltraten vom Typus Löffler, Léon-Kindberg, Kartagener usw. in Zusammenhang gebracht hat.

In Zusammenhang mit der Publizierung von vier Fällen eosinophiler Lungeninfiltrate hat Hedvall, 1942, eine Übersicht der damaligen Literatur gegeben.

Fall 1. 47jähr. Frau. Seit etwa 5 Jahren zeitweilig Bronchitis und Nasenbeschwerden. In den Jahren 1939, 1940 und 1941 hat die Patientin kürzere Perioden wegen *asthmatischer Bronchitis* in der Medizinischen Klinik gelegen, und sie ist während dieser Zeit wiederholt wegen *Sinusitis* und *Polypose* operiert worden. Bei diesen Gelegenheiten hatte sie etwa 16,000 Weisse und 4—6 % Bluteosinophilie.

Im Jahre 1938 traten *Gelenkbeschwerden* auf, die 4—5 Monate andauerten. Schmerzen sowie Anschwellung der Fussgelenke und Zehen behin-

derten sie beim Gehen. Mit der Zeit klangen die Symptome ab. Doch hat die Patientin seitdem bisweilen Gelenkschmerzen, besonders bei schlechtem Wetter.

Das letzte Jahr hat sie gearbeitet, doch hat sie, besonders nachts, viel husten müssen. Nach einem Trauma gegen den Brustkorb im Oktober 1942 begannen Schmerzen zwischen den Schulterblättern und im Kreuz aufzutreten.

Bei der Untersuchung in der Medizinischen Poliklinik am 26. 10. 1942 fand man eine Parenchymverdichtung in der linken Lunge, und vom 2. bis zum 23. 11. war die Frau dann unter der Diagnose *flüchtiger eosinophiler Lungeninfiltrate in der Medizinischen Klinik*.

Die Röntgenuntersuchung am 3. 11. zeigte unregelmässige, fleck- und strangförmige Parenchymverdichtungen basal in beiden Lungenfeldern, vorwiegend linksseitig; ausserdem diffuse und mehr fleckförmige Parenchymverdichtungen lateral im rechten I₄ sowie im linken Spitzenfeld.

Am 16. 11. war die Verdichtung im rechten I₄ verschwunden und die linksseitigen Veränderungen hatten an Ausdehnung und Intensität stark nachgelassen. Röntgendiagnose: Löffler-Infiltrate.

Physikalisch bestanden Rhonchi, doch keine sichere Dämpfung oder Veränderung der Atmungsgeräusche. Pos. Tuberkulinreaktion. In der Meerschweinchenprobe mit Magenspülflüssigkeit keine Tuberkelbakterien. Kein Sputum.

Bei wiederholten Untersuchungen wurden für die weissen Blutkörperchen Werte zwischen 22,000 und 14,400 gefunden, die Anzahl der Eosinophilen betrug 18.5—28 %. In den Fäzes keine Wurmeier. Die Senkungsgeschwindigkeit nahm von 40 auf 78 mm pro Stunde zu.

Der Allgemeinzustand war die ganze Zeit unberührt, die Frau hatte leichten Hustenreiz. Subfebrile Temperatur.

In den letzten Tagen traten Schnupfen und rechtsseitige Otitis hinzu. Die Patientin wurde deshalb am 22. 11. in die Ohrenklinik verbracht, wo sie drei Wochen wegen *akuter Otitis, Nebenhöhlenaffektion und Polypose* behandelt und dann symptomfrei entlassen wurde. Prof. Dohlman fand reichliche eosinophile Leukozyten im Ohrenfluor.

Während des Aufenthaltes in der Ohrenklinik, Mitte Dezember 1942, bekam die Kranke Schmerzen in Knie- und Fussgelenken. Die Gelenke waren druckempfindlich, geschwollen und gerötet. Die Beschwerden seitens der Gelenke verstärkten sich dann zu Hause, so dass die Frau die meiste Zeit bettlägerig war. Allmählich traten auch Schmerzen in Hand- und Fingergelenken mit Schwellung und Druckempfindlichkeit hinzu.

Ferner stellten sich gewisse Magenbeschwerden mit Schmerzen und saugenden Empfindungen im Epigastrium ein. Die ganze Zeit litt sie unter starkem Hustenreiz, ohne auswerfen zu können. Keine Asthmaanfälle. Sie lag zu Hause zu Bett,

bis sie am 2. Jan. 1943 wieder in die Medizinische Klinik aufgenommen wurde. Hier blieb sie 3 1/2 Monate.

Während dieses und des vorigen Krankenhausaufenthaltes zeigte die Patientin Eosinophilie und einwandfreie oder wahrscheinliche (mögliche) allergische Manifestationen mit folgenden Lokalisationen: 1) Ohr, 2) Lungen und obere Luftwege, 3) Gelenke, 4) Haut, 5) Herz, 6) Zentralnervensystem und 7) Magen-Darmkanal. Falls nichts anderes bemerkt, betreffen die Angaben im folgenden den zweiten Krankenhausaufenthalt.

1) *Otitis mit eosinophilem Fluor, Nebenhöhlenaffektionen (siehe oben).*

2) *Symptome seitens der Lungen und der oberen Luftwege, Blutveränderungen:* Nachstehend werden hauptsächlich Angaben über den röntgenologischen Lungenstatus gemacht, da die physikalischen Symptome, wie es bei eosinophilen Lungeninfiltraten der Fall zu sein pflegt, spärlich waren: ein etwas kürzerer Perkussionston über den infiltrierten Gebieten und verstreute Rhonchi über den Lungen. Mässiger Husten. Bei wiederholten Untersuchungen wurden eosinophile Leukozyten in mehr oder weniger reichlicher Zahl im spärlichen, farblosen *Auswurf* gefunden. Subfebrile *Temperatur*. Zum Blutstatus vgl. unten. In den Fäzes keine Wurmeier.

Rtg. 4. 1. 1943: Seit der Untersuchung am 4. 12. 1942 ist basal links eine grössere Parenchymverdichtung hinzugekommen.

12. 1. Ein ähnliches Infiltrat jetzt an der rechten Basis.

22. 1. Leichter Regress der basalen Parenchymverdichtungen. Sonst status quo.

Die Zahl der *weissen Blutkörperchen* war bei Bestimmungen in Abständen von etwa einer Woche (in Klammern die Prozentzahl der eosinophilen Leukozyten): 16,400 (33 %), 20,600 (42), 24,300 (41), 24,100 (52). Jetzt und auch weiterhin keine unreifen Formen. Im *Sternalpunktat* vom 23. 1. bei sonst normalen Verhältnissen 44 % eosinophile Elemente. Senkungsgeschwindigkeit 71—85 mm/1 Stde.

Die zuerst subfebrile Temperatur schien am 24. 1. ansteigen zu wollen. Hustenreiz mit spärlichem, farblosem Expektorat wie bisher. In zwei Sputumproben fanden sich *Pneumokokken vom Typus 31*. Von der Annahme ausgehend, dass es sich um eosinophile Bronchopneumonien handle, bekam die Frau in der Zeit vom 26. 1. bis zum 6. 2. *Sulfathiazol*, und zwar wie bei Pneumonie (am ersten Tage 4 + 4 g in einem Abstand von 4 Stunden, dann 6mal tägl. 1g; Blutkonzentration 5—8 mg %). Am zweiten Tage wurde die Temperatur wieder subfebril und blieb dies dann auch.

Rtg. 3. 2.: Vollständiger Regress der rechtsseitigen Veränderung. Die linksseitige Verdichtung bestand ziemlich unverändert fort.

9. 2.: Auch die linksseitige Verdichtung ist fast aufgehellt.

17. 2.: Die Verdichtung an der linken Basis hat weiterhin abgenommen.

20. 2.: Starke Schleimhautverdickung in sämtlichen Nebenhöhlen der Nase. — Die Patientin hatte über mässigen Schnupfen und Spannung im Gesicht geklagt.

Die Zahl der weissen Blutkörperchen (% eosinophile) betrug während dieser Zeit bei Bestimmungen in Abständen von etwa einer Woche: 11,400 (59 %), 17,200 (34), 11,500 (47), 14,500 (11.5), 9,600 (21.5).

Die folgende Kontrolluntersuchung der Lungen vollzog sich nach einem im voraus festgelegten Schema mit einer Röntgenuntersuchung etwa einmal wöchentlich. Die Beschwerden der Patientin verschlimmerten sich nicht, der Allgemeinzustand blieb unverändert, ebenso die Temperatur.

2. 3.: *Im oberen Teile des rechten Lungenfeldes sind Parenchymverdichtungen hinzugetreten*, und zwar teils im Spitzenfeld in einem handteller-grossen Gebiet, teils in einem kleineren Gebiet lateral im I₃.

Jetzt wurde eine neue Typenbestimmung der Bakterien im Sputum gemacht. Zwei Proben ergaben *Pneumokokken vom Typus 33*. Deshalb wurde eine nochmalige *Sulfathiazolkur* mit gleicher Dosierung wie bei der ersten durchgeführt, und zwar vom 4. 3. bis zum 11. 3. Blutkonzentration bis zu 6.6 mg %.

Die Temperatur war während dieser Zeit leicht subfebril, die Zahl der weissen Blutkörperchen höchstens 10,300, 35.5—36.5 % Eosinophilie.

Am 10. 3. zeigte das Röntgenbild einen starken Regress der Parenchymveränderungen in beiden Lungen, und bei einer weiteren Untersuchung am 12. 3. waren die Veränderungen so gut wie verschwunden. Spätere Kontrolluntersuchungen in Abständen von einer Woche erhoben negative Lungenbefunde.

Die Senkungsgeschwindigkeit verlangsamte sich allmählich auf 37 mm/1 Stde. Den folgenden Monat hindurch bestand eine zwar hohe, aber sinkende Eosinophilie, 43—7 %. Das Sputum wurde wiederholt auf *Pneumokokken* untersucht; in einer Probe fand man solche vom Typus 33, in den übrigen keine.

Nachdem das Allgemeinbefinden vorher recht gut gewesen war, traten am 12. 3. plötzlich *Bronchialasthmabeschwerden* auf, weshalb die Frau u. a. mit 10 % Adrenalin im Spray behandelt wurde. Ferner bekam sie Tabletten mit Agaricin, Papaverin, Theofyllin und Coffein (Astmolen «Leo»). Die Beschwerden liessen im Verlauf von zwei Wochen allmählich nach und klangen dann nach weiteren zwei Wochen völlig ab.

Aus Anlass einer Angabe Magnussons, 1938, Inhalation von Adrenalin habe eine sofortige, wenn auch vorübergehende Wirkung auf die Lungenveränderungen bei flüchtigen eosinophilen Lungeninfiltraten, wurden wiederholte Versuche mit dieser Therapie gemacht und die Wirkung durch Röntgendurchleuchtung kontrolliert. Die Adrenalininhalation hatte in diesem Falle keinen Effekt auf die Verdichtungen im Lungenparenchym.

3) *Gelenksymptome*: Beim Klinikeintritt Anfang Januar waren die Fuss- und Kniegelenke der Patientin mässig geschwollen mit örtlicher Wärme-steigerung und Bewegungsschmerzen, die gleichen Symptome in den Metakarpophalangealgelenken. Sie gab an, dass auch mehrere andere Gelenke schmerzten, doch waren objektiv keine Symptome festzustellen. Das Röntgenbild stellte keine pathologischen Veränderungen der betroffenen Gelenke fest.

Die Gelenkerscheinungen klangen im übrigen subjektiv und objektiv im Laufe der ersten 3—4 Wochen ab, doch klagte die Frau über hartnäckige subjektive Beschwerden an Hand- und Fussgelenken rechts während einer Zeit von zwei Monaten im Zusammenhang mit der weiter unten erwähnten Parese dieser Gliedmassen. Keine sicheren objektiven Gelenkbefunde während dieser Zeit.

4) *Hautsymptome*: Am Anfang der dritten Woche traten, im Zusammenhang mit erhöhten Beschwerden im rechten Fussgelenk, Petechien am rechten Unterschenkel und Fussrücken auf, die eine Woche lang bestanden. Ascorbinsäurebelastung lieferte keine Anhaltspunkte für Skorbut; keine Zahnfleischblutungen. Normale Thrombozytenzahl, bei Stauungsproben keine Blutungen.

5) *Herzsymptome*: Da der Puls der Patientin die ganze Zeit stark beschleunigt war, etwa 90 mit Spitzenwerten um 110, wurden wiederholt Elektrokardiogramme aufgenommen. Es waren keine physikalischen oder röntgenologischen Anzeichen eines Herzleidens festzustellen. Blutdruck um 120/80.

Schon bei dem ersten Klinikaufenthalt hatte das Ekg. ein wenig niedrige T-Zacken in sämtlichen Ableitungen gezeigt. Diagnose: Myokardschädigung (November 1942).

Wiederholte Ekg. während des letzten Klinikaufenthaltes zeigten ausgeprägtere Zeichen einer Myokardschädigung. 23. 1. 1943: T I schwach negativ, T II isoelektrisch und T IV negativ; Überleitungszeit 0.19, QRS-Zeit 0.08 Sek. 9. 2.: Überleitungszeit 0.16, sonst status quo. Der letztere Befund wurde auch bei Untersuchungen am 17. 2. und 9. 3. erhoben. Bei den folgenden Untersuchungen allmählich Normalisierung des Ekg.s bei bestehender Tachycardie.

6) *Symptome seitens des Zentralnervensystems*: Während des ersten Krankenhausaufenthaltes zeigte die Frau psychisch keine Besonderheiten. Ab Anfang Januar 1943 wurde jedoch allmählich eine allgemeine psychische Beeinflussung manifester. Sie wurde allmählich stumpf, »albern« und bekam ein Salbengesicht. In der zweiten Januarhälfte, als die objektiven Gelenkerscheinungen schon verschwunden waren, begann sie über Schmerzen im rechten Arm und Bein zu klagen, hauptsächlich in Hand und Fuss. Es wurden keine objektiven Befunde an den Gelenken erhoben, diese waren voll beweglich. Doch klagte die Frau über Schmerzen bei extremen Bewegungen des Fussgelenks. In der rechten Körperhälfte hatte sie auch das Gefühl des Eingeschlafenseins. Anfang Februar konstatierte man eine einwandfreie mässige Parese und Rigidität vom extrapyramidalen Typus im rechten Arm und Bein. Die Frau konnte mit der rechten Hand nicht gut greifen und konnte nicht mit dem rechten Fuss auftreten. Sehnen- und Periostreflexe am rechten Arm sowie der rechte Patellarreflex schwächer als links. Fragliche Sensibilitätsbeschränkung in der rechten Fussregion. Herabgesetzte Stereognose an der rechten Hand. Nervensystem im übrigen o. B.

Die Lumbalpunktion erhob folgende Befunde: Druck 60 mm. Nonne und Pandy pos. Bisgaardsche Eiweissreaktion in der Verdünnung 1:10 pos. 9 Zellen pro mm³ Liquor: 2 Lymphozyten und 7 Leukozyten, darunter 50 % eosinophile (34 % Bluteosinophilie).

Der konsultierte Psychiater (Dr. Ring Lundquist) fand am 8. 2. psychische Veränderungen, die wohl vereinbar waren mit denen bei einem organischen Nervenleiden, Enzephalitis.

Dem Gutachten ist folgenden Analyse beigegeben:

Nach der Kretschmerschen Typenlehre gehört sie zu den zyklithymen. Vom Gesichtswinkel der Sjöbringschen Konstitutionslehre aus ist sie eine relativ gut begabte (normo- oder leicht superkapable), im übrigen aber primitive Frau. Sie ist sicher substabil, neigt also zu Verstimmungszuständen, ferner ist sie leicht subsolid (also etwa eine leicht »hysterische« Konstitution) und wahrscheinlich leicht subvalid (asthenisch).

Unter schwierigen äusseren Verhältnissen besteht also die Möglichkeit, dass sich auf den Gebieten der verschiedenen Radikale psychische Insuffizienzerscheinungen einstellen können. Der Zustand lässt im übrigen nicht auf schwerere solche Insuffizienzerscheinungen schliessen.

Während der folgenden beiden Monate trat eine langsame Besserung des psychischen Zustandes ein, die Rigidität verschwand und die Kraft kehrte in der gelähmten Seite zurück, zuletzt im Bein. Auch die Schmerzen nahmen ab. Als die Lumbalpunktion einen Monat später wiederholt wurde, war der Liquor normal.

7) *Symptome seitens des Magen-Darmkanals:* Während der ersten Wochen des letzten Klinikaufenthaltes hatte die Patientin ausgesprochene Beschwerden im Epigastrium mit Schmerzen im Anschluss an die Mahlzeiten und je nach der Art der genossenen Speisen, so dass sie u. a. keine fetten oder gebratenen Speisen und auch keinen Kaffee vertragen konnte. Die Beschwerden, die durch Papaverin gelindert wurden, verschwanden nach einer 2—3wöchigen Diätkur.

In Anbetracht des Charakters der Schmerzen wurden Oesophagus, Magen und Duodenum röntgenuntersucht und die Cholecystographie gemacht, wobei normale Befunde erhoben wurden. Auch fraktioniertes Probefrühstück, Galaktosebelastung, Bilirubin und Zitronensäure im Serum o. B.

Zusammenfassung von Fall 1.

47jährige Frau, die seit etwa 5 Jahren Bronchitis hat. In den Jahren 1939—1941 wiederholt wegen asthmatischer Bronchitis im Krankenhaus. Bei diesen Gelegenheiten 4—6% Eosinophilie, Sinuitis und Polypose. 1938 4—5 Monate lang Gelenksymptome.

Im November 1942 wegen flüchtiger eosinophiler Lungeninfiltrate und bis zu 28 % Eosinophilie im Krankenhaus. Fortgesetzte Behandlung in der Ohrenklinik während einer Zeit von drei Wochen

wegen akuter Otitis mit eosinophilen Leukozyten im Fluor sowie Polypose. (Prof. Dohlmän hat früher gezeigt, dass das Sekret bei Otitiden oft zahlreiche eosinophile Leukozyten enthält.) Gelenkerscheinungen traten hinzu.

Während der folgenden Monate zeigte die Kranke in der Klinik folgende Symptome, von der eben genannten 1) Otitis abgesehen: 2) Seitens der Lungen mässige Bronchitiserscheinungen und wiederholte Schübe von Lungeninfiltraten mehr oder weniger flüchtigen Charakters nebst Bluteosinophilie bis zu 59 %. Das Sternalpunktat war normal. Zweimal wurde Sulfathiazoltherapie eingeleitet, nachdem bei verschiedenen Untersuchungen Pneumokokken vom Typus 31 bzw. 33 konstatiert worden waren. Im Anschluss an diese Therapie gingen die Lungenveränderungen schnell zurück. Trotz der früheren Schwankungen der Lungenbilder im übrigen ist doch die Wirkung des Sulfathiazols wahrscheinlich. Eine Schrifttumsangabe, dass die eosinophilen Lungeninfiltrate durch Inhalation von Adrenalin beeinflusst würden, konnte nicht bestätigt werden. 3) Gelenkrheumatismus, 4) Purpura, 5) Tachykardie und Symptome einer Myokardschädigung, die mehrere Monate hindurch bestanden, 6) Enzephalitis mit vorübergehender halbseitiger Parese und extrapyramidaler Rigidität; eosinophile Leukozytose im Liquor cerebrospinalis, und 7) gewisse diagnostisch dunkle Symptome seitens des Magen-Darmkanals.

Bei der Beurteilung der verschiedenen Symptome erhebt sich die Frage, ob diese auf eine und dieselbe Krankheit zurückgehen. Die Lungeninfiltrate treten bei einer Asthmatikerin mit schon vorhandener Bereitschaft für Eosinophilie auf. Doch liegt keine konstitutionelle Eosinophilie vor und ebenfalls keine eosinophile Leukämie. Gelenkrheumatismus mit Myokardschädigung und Purpura sieht man häufig in dieser Konstellation. Auch Enzephalitiden können — wenn auch selten — im Zusammenhang mit rheumatischen Infektionen auftreten. Die Symptome seitens des Verdauungstraktes sind diagnostisch unklar.

Es erscheint doch am ansprechendsten, sämtliche Symptome unter einer Krankheit zusammenzufassen. Von den v. Meyenburgschen Befunden ausgehend, dass eosinophile Infiltrationen auch an anderen Stellen als in den Lungen vorkommen, liegt die Annahme nahe, dass diese verschiedenen Symptome, die jedes für sich durch Allergie-eosinophile Infiltrate bedingt sein können,

in ihrer Ausdrucksform durch die unterschiedlichen Lokalisationen verschieden geprägte Erscheinungen eines und desselben Krankheitsprozesses sind.

Die v. Meyenburgschen Ergebnisse machen es wahrscheinlich, dass die Lungeninfiltrate auch in dem vorliegenden Fall Pneumonien sind. Das Vorkommen von Pneumokokken im Hustenauswurf braucht natürlich nicht zu bedeuten, dass es sich um von den nachgewiesenen Typen verursachte eosinophile Bronchopneumonien handelt. Falls die Annahme, dass die übrigen klinischen Symptome durch eosinophile Infiltrate bedingt sind, zutrifft, würde hämatogene Ausbreitung von den primären Bronchopneumonien oder zu irgendeinem Fokus sekundären Herdpneumonien denkbar sein.

Es ist natürlich auch an Periarteriitis nodosa zu denken: es gibt aber u. a. keine Lymphozytose, keine Augen- oder Nierensymptome, normalen Blutdruck, flüchtige-reversible Veränderungen. Nach Klinge und Ehrström ist P. n. eine irreversible allergische Reaktion im Gefäßsystem.

Der vorstehend geschilderte Fall hat besonderes Interesse 1) wegen des wahrscheinlichen multilokulären Vorkommens eosinophiler Infiltrate, 2) wegen des Vorkommens von Pneumokokken im Sputum, 3) wegen des wahrscheinlichen guten Effektes der Chemotherapie auf die Lungeninfiltrate (die eosinophilen Bronchopneumonien?), 4) wegen des Vorkommens rheumatischer Gelenkerscheinungen und 5) wegen des Vorkommens einer Otitis.

Fall 2. 36jähr. Frau. Seit 1926 litt sie recht viel unter Hustenreiz, seit 1937 dann und wann Atemnot in Zusammenhang mit dem Husten.

1940 lag sie mehrer Monate mit Fieber zu Bett und sie wurde auch im Krankenhaus gepflegt.

Flüchtige Lungeninfiltrate mit 7—47 % Bluteosinophilie.

Seit der Entlassung aus dem Krankenhaus sind die Lungen wiederholt kontrolliert und für gesund befunden wurden, doch nicht während der zwei letzten Jahre. Die Frau hatte jedoch die ganze Zeit Husten und Atemnot, aber keine asthmatischen Beschwerden. In den Jahren 1940—41 Sputummengen bis etwa 600 cm³ pro Tag, später etwa 150—250 cm³. Im letzten Jahr fühlte sie sich subjektiv bedeutend wohler.

Am 14. Januar 1943 bekam die Patientin bei tiefem Atmen plötzlich Stiche im linken Teil der Brust. Anfangs leichte Temperatursteigerung, nach einer Woche Fieber bis zu 38.5°. Die Sputummengen vermehrten sich auf etwa 500 cm³ pro Tag. Seit Anfang Februar verschlimmerte sich das Befinden, die Atembeschwerden verstärkten sich. 4 Tage vor dem

Klinikeintritt stellte ein Arzt Dämpfung und Verdacht auf Pneumonie fest. Auf Anraten des Verfassers keine Therapie. Am 23. 2. 1943 kam die Frau in die Medizinische Klinik.

Der Allgemeinzustand war mässig in Mitleidenschaft gezogen, die Kranke klagte über lästigen Husten. Physikalisch fand man eine Dämpfung in der rechten Spitzenpartie und über dem grösseren Teil der linken Lunge, trockene Rasselgeräusche, doch keine Bronchialatmung. Dem entsprach der Röntgenbefund ausgedehnter Lungeninfiltrate, vornehmlich linksseitig. — Weisse Blutkörperchen 10,600, 24 % Eosinophilie. Senkungsgeschwindigkeit 78 mm/1 Stde. Tuberkulinreaktion pos.

In der ersten Woche war der Zustand unverändert, subfebril-febril. Sputum bis zu 320 cm³ pro Tag, doch reichlich mit Speichel vermischt. Eosinophile Leukozyten im Sputum. Anzahl der weissen Blutkörperchen 9,600 und 10,000, 32 bzw. 20.5 % Eosinophilie. Keine Wurmeier in den Fäzes. Tuberkulinreaktion positiv. Keine Tuberkelbazillen im Sputum.

Rtg. 3. 3.: Stärkere Verdichtung links basal, sonst status quo.

Zwei Sputumuntersuchungen an verschiedenen Tagen hatten Pneumokokken vom Typus 7 gezeigt. Daraufhin Sulfathiazolkur, am ersten Tage 4 + 4 g, in einem Abstand von 4 Stunden, dann 1 g 6mal täglich. Sulfathiazolkonzentration im Blut etwa 7—9 mg %. Nach einwöchiger Sulfathiazolbehandlung hatte sich der Allgemeinzustand gebessert, der Husten liess nach und die tägliche Sputummenge betrug nur etwa 20 cm³. Das Röntgenbild zeigte am 9. 3. einen solchen Regress der doppelseitigen Verdichtungen, dass nur noch geringfügige Reste übrig waren. Bei abermaliger Kontrolle eine Woche später, am 15. 3., waren alle die aktuellen Lungenveränderungen verschwunden.

Während der Woche der Sulfathiazolkur wurde die Temperatur normal, die Zahl der weissen Blutkörperchen war 8,000 (21.5 % Eos.) und 9,800 (16 %). Auch die folgenden Wochen hielt die Eosinophilie an.

Nach Beendigung der Sulfathiazolbehandlung und nach verschwinden der Lungenveränderungen hustete die Kranke immer noch ein wenig, doch mit nur wenig, wie bisher farblosem Expektorat. Wiederholte Sputumuntersuchungen fanden keine Pneumokokken.

Zusammenfassung von Fall 2.

Eine 36jährige Frau hat seit etwa 15 Jahren Reizhusten, »Kitzeln« im Halse. Im Jahre 1940 wegen eosinophiler Lungeninfiltrate mit anfangs 7 %, später bis zu 47 % Eosinophilie im Krankenhaus. Anschliessend Husten mit grossen Sputummengen, doch keine asthmatischen Beschwerden.

Nachdem sie einen Monat lang Fieber gehabt hatte, lag sie 1943 mit ausgedehnten eosinophilen Lungeninfiltraten und bis zu 32 % Eosinophilie in der Medizinischen Klinik. Nachdem die Infiltrate

eine Woche lang konstant geblieben oder etwas grösser geworden waren und man bei zwei Sputumuntersuchungen Pneumokokken vom Typus 7 gefunden hatte, bekam die Patientin Sulfathiazol. Während der Sulfathiazolkur verschwanden die Infiltrate binnen einer Woche fast völlig und die Temperatur wurde normal.

Das Rezidiv der eosinophilen Lungeninfiltrate dürfte entweder so zu erklären sein, dass der Organismus die ganze Zeit die Neigung gehabt hat, eosinophil (gegen Infektionen der Luftwege?) zu reagieren, oder so, dass eine solche Neigung wiedergekehrt ist. Bei der ersten Erkrankung vor drei Jahren sind die Sputa nicht auf Pneumokokken untersucht worden, so dass nichts darüber ausgesagt werden kann, ob der Infektionsstoff (das Allergen) in beiden Fällen das gleiche gewesen ist. Der positive Bakterienbefund sichert natürlich nicht die Pneumokokken als Ursache der Lungenveränderungen. Doch ist es — im Hinblick auf v. Meyenburgs Untersuchungen — wahrscheinlich, dass es sich wenigstens bei der letzten Erkrankung um eosinophile Bronchopneumonien gehandelt hat.

Dieser Fall ist von Interesse 1) wegen des Rezidivs eosinophiler Lungeninfiltrate nach drei Jahren, 2) wegen des Vorkommens von Pneumokokken im Sputum und 3) wegen der wahrscheinlich guten Wirkung einer Sulfathiazolkur auf die Lungenveränderungen (die eosinophilen Bronchopneumonien?).

Fall 3. 47jähr. Frau. Mit 5 Jahren Sekretion aus dem rechten Ohr, das 1922 radikaloperiert wurde. Keine völlige Heilung, sondern zuzeiten Ohrenfluss.

Seit 1932 *Bronchitis asthmatischen Typs*. Diese Krankheit führte sie 1935 und 1941 ins Krankenhaus. Lungenröntgenbild o. B. 3 % Bluteosinophilie. Zur gleichen Zeit auch Schnupfen, der sich nach einer Kieferhöhlenoperation 1938 besserte.

Im Juni 1941 plötzlich auftretende *Gelenkschmerzen* ohne vorherige Erkältung; Fuss-, Zehen-, Finger- und Kniegelenke waren druckempfindlich und leicht geschwollen. Die Patientin fühlte sich fieberig, mass aber die Temperatur erst 10 Tage später und hatte nun 38—38.9°. Sie lag zwei Wochen zu Hause zu Bett und war dann im Sommer 1941 zwei Wochen in der Klinik. Während der ersten Tage in der Klinik subfebrile Temperatur, dann fieberfrei. Senkungsgeschwindigkeit 3 mm/1 Stde. Zahl der weissen Blutkörperchen 5,100, 5 % Eosinophile. Keine objektiven Gelenkbefunde.

Während des folgenden Winters und auch Sommers verursachten ihr die genannten Gelenke zeitweilig erhebliche Beschwerden; die Gelenke waren druckempfindlich, leicht angeschwollen und schmerzten bei Bewegungen. Zeitweilig war die Frau beträchtlich in ihrer Arbeit behindert.

Am 8. 10. 1942 kam sie aus der Ohrenklinik, in der sie wegen ihrer Rhinitis drei Wochen lang gewesen war, in die Medizinische Klinik und wurde hier vom 8. 10. bis zum 26. 11. wegen eosinophiler Lungeninfiltrate behandelt.

Lungensymptome: physikalisch bestehen Zeichen, die auf ein Emphysem schliessen lassen, und reichliche Rhonchi. Keine Dämpfung.

Rtg. am 10. 10. 1942: Beide Lungenfelder zeigen eine mässig verstärkte, strangförmige Zeichnung. Ausserdem in der oberen Hälfte des rechten Lungenfeldes eine fleckige Parenchymverdichtung.

25. 10.: Die Parenchymverdichtung im rechten Lungenfeld ist verschwunden. Im linken I_1 ist lateral eine kleinere Verdichtung hinzugetreten.

5. 11. (Durchleuchtung): Der Prozess im linken I_1 hat abgenommen, im linken I_2 ist ein neuer aufgetreten.

10. 11.: Auch die zuletzt aufgetretene Parenchymveränderung ist jetzt verschwunden. — Röntgendiagnose: Löffler-Infiltrate.

Positive Tuberkulinreaktion. Im *Sputum* keine Tuberkelbazillen, Meerschweinchenprobe negativ. Einige Male eosinophile Leukozyten, bei den übrigen Untersuchungen nihil in dem spärlichen Sputum.

Der *Allgemeinzustand* war die ganze Zeit unberührt. Die Patientin litt anfangs unter Husten und recht viel Kopfschmerzen, die bei psychiatrischer Konsultation als allergisch bezeichnet wurden. Die Lumbalpunktion erhob normale Befunde.

Die *Temperatur* war die ersten Tage subfebril, dann normal, bis am 22. 10. wieder eine leicht subfebrile Temperatur vorlag, die für die Dauer von 2 Tagen bis auf 39° anstieg, offenbar im Zusammenhang mit dem Auftreten des neuen Infiltrats, das am 5. 11. konstatiert wurde. Die bisher normale Anzahl *weisser Blutkörperchen* stieg dabei auf 14,300. Eine bzw. zwei Wochen später betrugen die Werte 15,300 bzw 7,300. Die Zahl der eosinophilen Elemente war bei den letztgenannten Zählungen 4 bzw. 4.5 %, bei den übrigen Zählungen im Krankenhaus 10, 9, 9, 6 und 6 %.

Senkungsreaktion: am 8. 10. 77 mm/1 Stde., 15. 10. 37, 22. 10. 18, 28. 10. 20, 7. 1. 53, 16. 11. 21 und bei der Entlassung 22 mm/1 Stde.

Anfangs leichte Anämie (Hämoglobin 75 %, rote Blutkörperchen, 4.1 Mill.), die sich in den folgenden Wochen besserte.

Elektrokardiogramm normal.

Die Patientin wurde auch subjektiv symptomfrei entlassen und hat seitdem (Jan. 1943) keinerlei Beschwerden seitens der Luftwege oder Gelenke gehabt.

Zusammenfassung von Fall 3.

Eine 47jährige Frau mit chronischer Otitis seit dem fünften Lebensjahr und einer Bronchitis asthmatischen Typs seit 10 Jahren bekommt im Anschluss an eine Otitis flüchtige Lungeninfiltrate des Löfflerschen Typs, verbunden mit Bluteosinophilie bis zu 10 %.

Während der vorangegangenen 18 Monate hatte sie rheumatische Gelenkerscheinungen, die aber beim Auftreten der Lungenaffektion abgeklungen waren. Der Lungenprozess ging mit Kopfschmerzen einher. Normaler Liquor cerebrospinalis.

Neben den eosinophilen Lungeninfiltraten sind an diesem Fall von Interesse 1) das Vorkommen von Gelenkerscheinungen und 2) das Vorkommen einer Otitis.

Fall 4. 41jähr. Frau. Seit ungefähr 1938 Asthma bronchiale. Als sie 1939 wegen ihrer Beschwerden im Krankenhaus war, entdeckte man einige Lungenherde, die indessen seit 1933, wo die Patientin Erythema nodosum gehabt hatte, unverändert fortbestanden hatten. Sorgfältige Observationen lieferten keine Anhaltspunkte für aktive Tb. Bei dieser Gelegenheit hatte sie auch Zeichen einer chronischen Sinuitis.

Von einer beschwerlichen Periode im Herbst 1939 abgesehen, verursachte ihr das Asthma bis August 1942 fast keine Beschwerden. Jetzt traten schwere Anfälle auf und ausserdem litt sie unter starkem Husten. Im September zeitweilig leichtes Fieber. Seit dem Wiederauftreten des Asthmas im August meist bettlägerig.

Vom 20. 10. 1932 bis zum 8. 1. 1943 war sie wegen Asthma bronchiale und eosinophiler Lungeninfiltrate in der Medizinischen Klinik.

Lungensymptome: Die Röntgenuntersuchungen zeigten am 22. 10. 1942: grössere wolkige Verdichtung links basal lateral, kleinere Herde im I₂ und I₃ sowie im rechter I₄.

5. 11.: Die Verdichtung im linken I₁ hat etwas abgenommen. Basal im rechten Lungenfeld sind ein paar ähnliche Veränderungen hinzugetreten.

20. 11.: Regress der Veränderungen in der linken Basis. Am unteren Teil des linken Hilusgebietes ist ein kleinerer Fleck hinzugekommen.

27. 11.: Die zuletzt aufgetretene Veränderung hat sich stark vergrössert.

3. 12.: Aufhellung des Fleckes am linken Hilus.

10. 12.: Weitere Aufhellung.

5. 1. 1943: Die Infiltrate sind praktisch völlig verschwunden.

Röntgendiagnose: Löffler-Infiltrate.

Elektrokardiogramm normal.

Den röntgenologischen Lungenbefunden entsprach bei der physikalischen Untersuchung eine geringfügige oder unsichere Dämpfung; die Auskultation wurde von den asthmatischen Rhonchi beherrscht.

Sputum: Bei wiederholten Untersuchungen zahlreiche eosinophile Leukozyten. Der Versuch einer Lungenpunktion misslang, da die Patientin kollabierte.

Blut: Die Zahl der weissen Blutkörperchen betrug in den ersten drei Wochen 13,500; dann lagen die Werte zwischen 9,700 und 11,100. Die ganze Zeit 35—19 % Eosinophilie, und zwar mit den höchsten Werten zu Anfang; Zählung in der Regel einmal wöchentlich. Die Sternalpunktion

Der Fall hat Interesse wegen des Vorkommens rheumatischer Gelenksymptome bei einer Patientin mit eosinophilen Lungeninfiltraten.

Zusammenfassung.

Der Verf. teilt vier Fälle von Lungeninfiltraten mit Bluteosinophilie mit.

Der eine Fall weist klinische Symptome auf, die ähnliche Reaktionen seitens mehrerer Gewebe und Organe vermuten lassen.

In zwei Fällen sind bestimmte Pneumokokkentypen im Sputum festgestellt worden; ihre ätiologische Bedeutung wird erörtert. Die beiden genannten Fälle sind, die eine Patientin zweimal, mit augenscheinlich vorzüglichem Ergebnis mit Chemotherapie angegangen worden.

Drei Fälle wiesen rheumatische Gelenkerscheinungen auf.

In einem Fall haben die Lungenveränderungen nach dreijährigem freiem Intervall rezidiert.

Die Bedeutung der obigen Befunde wird erörtert.

Das Suchen nach Pneumokokken im Sputum, Chemotherapie und in resistenten Fällen evtl. spezifische Serumtherapie sind mit Rücksicht auf die vorliegenden präliminären Resultate — bis weitere Erfahrungen gesammelt sind — zu empfehlen.

Das wichtigste Bildmaterial der Fälle 1 und 2 wird in der Schweiz. med. Wschr. und Nordisk Medicin (im Druck) vorgelegt.

Literatur.

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Über die Histopathologie des »Pylorusdrüsenorgans« bei perniziöser Anämie.

Von

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Über siebzig Jahre hat die perniziöse Anämie der wissenschaftlichen Forschung getrotzt. Schon 1871 wies Biermer in seinem berühmten Vortrag darauf hin, dass zu dem Krankheitsbild Störungen im Verdauungskanal gehörten. Seitdem haben die Forscher dem Digestionsapparat ihr Interesse zugewandt. Die Krankheit führte früher zum Tode. Es bereitete daher keine Schwierigkeiten, für die pathologisch-anatomische Untersuchung erforderliches Material zu beschaffen, aber das histologische Bild war nicht leicht zu deuten. Die kadaverösen Prozesse schreiten schnell im Magen und in den Därmen vorwärts. Durch Ausdehnung und Zerfallsprozesse bekommt die Schleimhaut ein Aussehen, das früher allgemein als Atrophie angesprochen wurde. »Anadenie« in der Magenschleimhaut und Atrophie in der Darmschleimhaut wurden darum mit der Genese der perniziösen Anämie in Zusammenhang gebracht.

Durch Einspritzung von Formaldehydlösung in die Bauchhöhle unmittelbar nach dem Tode konnten Faber und Bloch kadaverösen Veränderungen vorbeugen. Es ergab sich dabei, dass im Darm

keine Atrophien vorhanden und dass die pathologischen Prozesse im Magen früher bedeutend übertrieben worden waren. Eine hochgradige Gastritis und ein verändertes Aussehen des Drüsenapparats konnten jedoch nach wie vor festgestellt werden. Eine pathologisch veränderte Magenschleimhaut ist seitdem zum typischen Bild der perniziösen Anämie gerechnet worden.

Das Interesse konzentrierte sich nunmehr auf die abnorme Bakterienflora im Darm, die bei Patienten mit perniziöser Anämie beobachtet wurde, und auf die Fälle der Krankheit, die wahrscheinlich durch Darmstrikturen oder durch die Anwesenheit von *Bothrioccephalus latus* im Darmkanal verursacht wurden. Man dachte sich, die Anämie werde durch toxische Substanzen verursacht, die durch die Darmwand resorbiert seien.

Einen Wendepunkt in der Forschung bezeichnet die von Minot und Murphy eingeführte Lebertherapie. Seitdem aus den Versuchen von Castle hervorgegangen war, dass sich im Magen des gesunden Menschen ein antianämischer Faktor bildet, der nicht im Magen von Patienten mit perniziöser Anämie anzutreffen ist, war die Frage nach der Rolle, die der Verdauungskanal bei der Genese der perniziösen Anämie spielt, wieder hochgradig aktuell geworden.

Meulengracht und seine Mitarbeiter hatten gezeigt, dass sich der antianämische Faktor beim Schwein in den Pylorusdrüsen im Magen und in den Brunnerschen Drüsen im Duodenum bildet. Meulengracht führte daher die Bezeichnung Pylorusdrüsenorgan als gemeinsamen Namen dieser beiden Drüsen ein.

Als in der menschlichen Pathologie von den Erfahrungen Gebrauch gemacht wurde, die bei den Versuchen mit Schweinemagen gewonnen worden waren, lag die Annahme nahe, dass das Pylorusdrüsenorgan bei der perniziösen Anämie Sitz krankhafter Veränderungen sei. Bei der histopathologischen Untersuchung des Pylorusdrüsenorgans aus 8 Fällen von perniziöser Anämie kam Meulengracht jedoch zu dem überraschenden Resultat, dass das Pylorusdrüsenorgan »recht intakt« erschien. Diese Auffassung erhielt eine Stütze durch Untersuchungen, die von Magnus und Ungley ausgeführt wurden. In 7 Fällen von perniziöser Anämie fanden diese Forscher keine Andeutung einer Atrophie oder entzündlicher Veränderungen in der Schleimhaut des Pylorus oder des Duodenums, und auch die Brunnerschen Drüsen liessen nichts

Abnormes erkennen. Die Ergebnisse der eben erwähnten Untersuchungen sind eigenartig und stehen teilweise im Widerspruch mit der früher herrschenden Auffassung, nach der auch die Schleimhaut des Pylorusteils Sitz entzündlicher und atrophischer Veränderungen ist, obwohl die pathologischen Prozesse hier weniger ausgeprägt sind als im Fundusteil.

In einer vor zwanzig Jahren ausgeführten Untersuchung von 16 Magen aus Fällen von perniziöser Anämie konnte der Verfasser dieser Zeilen die obigen Forschungsergebnisse bestätigen. Meine Untersuchung bezog sich indes auf die Schleimhaut des ganzen Verdauungskanals, und das Interesse konzentrierte sich auf die Veränderungen in der Zunge, dem Ösophagus und den Därmen. Der Vollständigkeit halber war jedoch auch der Magen durchgemustert worden, obgleich unter den Forschern, die die postmortalen Veränderungen in der Schleimhaut eliminieren konnten, Einstimmigkeit über die Histopathologie des Magens zu herrschen schien. Bei meiner Untersuchung wurden sowohl Präparate aus dem Pylorus als aus dem Fundus durchgesehen, aber wegen der damals bestehenden Ansicht über die Genese der Krankheit wurde den verschiedenen Abschnitten des Magens nicht die gebührende Aufmerksamkeit geschenkt. Auch die Brunnerschen Drüsen im Duodenum wurden nicht genauer untersucht.

Da die Histologie des Magens und Duodenums bei perniziöser Anämie wieder in den Brennpunkt der wissenschaftlichen Forschung getreten ist, ist es mir gerechtfertigt erschienen, mein in Paraffin eingebettetes Material noch einmal durchzumustern, um die neue Auffassung über das Aussehen des Pylorusdrüsenorgans nachzuprüfen.

Kasuistik.

Das mir zur Verfügung stehende Material umfasst 16 Fälle von perniziöser Anämie, von denen vor mehr als 20 Jahren Proben entnommen worden sind. Ausserdem habe ich 2 Fälle untersuchen können, die unlängst im Maria-Krankenhaus obduziert wurden. Dem Chefarzt der medizinischen Abteilung, Herrn Prof. F. Saltzman, spreche ich hier meinen Dank für die Überlassung des Materials aus. Es haben mir also zusammen 18 Fälle von perniziöser Anämie vorgelegen. Von diesen sind 17 nicht mit Leber- oder Magenpräparaten behandelt worden, während ein Fall mehrere Jahre lang eine solche Therapie durchgemacht hat.

Um postmörtale Veränderungen auszuschliessen, wurde das Material sobald wie möglich nach dem Tode aufbewahrt. In 2 Fällen wurde unmittelbar post mortem Formaldehydlösung nach Faber und Bloch in die Bauchhöhle eingespritzt. Als Kontrollfälle wurden zwei Magen von Personen, die eines gewaltsamen Todes gestorben waren, 3 Fälle von hochgradiger Anämie nicht- perniziöser Natur und ein Fall von tuberkulöser Meningitis verwertet. Der Raumersparnis halber wird hier nur ein kurzer Auszug aus den früher veröffentlichten Krankengeschichten und Sektionsprotokollen wiedergegeben. Die Numerierung der Fälle ist dieselbe wie in meiner früheren Arbeit. Nur die Fälle 17 und 18, die früher zwei aplastische Anämien darstellten, sind mit den vor kurzem zurückbehaltenen Fällen von perniziöser Anämie vertauscht worden.

Da die mikroskopischen Befunde vielleicht auf verschiedene Weise gedeutet werden können, habe ich mich gezwungen gesehen, hier eine neue Beschreibung der einzelnen Fälle zu geben.

Fall 1. 40jährige Frau, aufgenommen 29. 11. 1913, gestorben 31. 1. 1914. *Klinische Diagnose: Anaemia perniciosa.* 20. 1. 1914. Hb 26. Die Sektion, 5 Stunden nach dem Tode, bestätigt die klinische Diagnose. Aus dem Sektionsprotokoll: Magen ziemlich klein. Magenwand nicht besonders dünn. Schleimhaut glatt, mit punktförmigen Blutungen.

Pylorus. Das Oberflächenepithel ist nur teilweise erhalten. Die Zellen zeigen nichts Abnormes. Pylorusdrüsen sind in reicher Menge zu sehen. Stellenweise finden sich jedoch Lücken zwischen den Drüsen, und diese sind in Gruppen angesammelt, in denen die Drüsengänge einen unregelmässigen Verlauf zeigen. Die Zellen sind sekretgefüllt. Überall sieht man eine diffuse Infiltration mit Lymphozyten und Plasmazellen. Spärlich eosinophile und neutrophile Granulozyten.

Fundus. Die oberste Schicht der Schleimhaut durch kadaveröse Veränderungen zerstört. Es wird jedoch ersichtlich, dass die Drüsen kurz sind, unregelmässig verlaufen und weit auseinander liegen. Keine Deckzellen. Es sind mehrere Lieberkühnsche Krypten anzutreffen. Lymphozyten und Plasmazellen zeigen sich überall in der Tunica propria in reicher Menge nebst einzelnen eosinophilen und neutrophilen Granulozyten.

Zusammenfassung. Im Pylorus deutliche entzündliche Veränderungen, eine Andeutung von Drüsenatrophie und eine Umgruppierung der Drüsen. Im Fundus deutliche entzündliche Veränderungen, hochgradige Drüsenatrophie und Drüsenatypie.

Duodenum. Die Brunnerschen Drüsen zeigen nichts Abnormes:

Fall 2. 60jähriger Bauer, aufgenommen 20. 1. 1914, gestorben 1. 2. 1914. *Klinische Diagnose: Anaemia perniciosa.* 30. 1. 1914. Hb 16. Die

Sektion, 24 Stunden nach dem Tode, bestätigt die klinische Diagnose. Aus dem Obduktionsprotokoll: Magenschleimhaut blass und glatt. Magenwand dünn, besonders im Fundus.

Pylorus. Oberste Schicht der Schleimhaut kadaverös verändert. Die Drüsen liegen weit auseinander und bilden Gruppen unregelmässig verlaufender Drüsengänge. Es treten mehrere Darmkrypten auf. Reichlich Lymphozyten und Plasmazellen überall in der Tunica propria. Zahlreiche Russellsche Körperchen in der obersten Schicht.

Fundus. Schleimhaut kadaverös verändert. Drüsen kurz, weit auseinanderliegend; Deckzellen sind nicht zu finden. Überall in der Tunica propria reichlich Lymphoidzellen, stellenweise auch in der Muscularis mucosae.

Zusammenfassung. Im Fundus und Pylorus deutliche entzündliche Veränderungen sowie hochgradige Drüsenatrophie, besonders im Fundus.

Duodenum. Zwischen den Drüsengängen in den Brunnerschen Drüsen sieht man in etwas vermehrter Menge feinfaseriges Bindegewebe.

Fall 3. 34-jähriger Arbeiter, aufgenommen 3. 3. 1914, gestorben 13. 3. 1914. *Klinische Diagnose:* *Anaemia perniciosa.* Enteritis acuta. 13. 3. 1914. Hb 17. Die Sektion, 11 Stunden nach dem Tode, bestätigt die klinische Diagnose.

Pylorus. Schleimhaut von gewöhnlicher Dicke. Die Foveolae gastricae dringen bis in halbe Tiefe der Schleimhaut hinab. Oberflächenepithel bewahrt, die Zellen enthalten an mehreren Stellen auffallend reichlich Sekret.

Drüsen finden sich ungefähr in derselben Menge wie in den Kontrollfällen. Ihr Verlauf ist nicht ganz regelmässig, sondern sie sind etwas verschoben und stellenweise etwas geschlängelt. An manchen Stellen ist das Bindegewebe zwischen den Drüsengruppen etwas vermehrt und die kollagenen Fasern auffallend grob. Die Drüsenzellen sind nur ausnahmsweise sekretgefüllt. Einzelne Deckzellen sind hier und da in den Drüsengängen anzutreffen. Lymphozyten und Plasmazellen zeigen sich reichlich unter dem Oberflächenepithel, aber auch tiefer in der Schleimhaut, an manchen Stellen vermehrt.

Fundus. Das Oberflächenepithel fehlt. Die Foveolae gastricae erstrecken sich bis halbwegs zur Muscularis mucosae hinab. Die Drüsen sind kurz, verkümmert und an manchen Stellen etwas erweitert. Deckzellen sind anzutreffen, wiewohl in geringerer Zahl als normalerweise. Mancherorts sind die Drüsenböden aus hellen sekretgefüllten Zellen aufgebaut. Die Drüsen liegen weiter voneinander entfernt als normal. Das Bindegewebe zwischen ihnen ist feinfaserig und locker. Lymphozyten und Plasmazellen kommen in dem interstitiellen Gewebe in reicher Menge vor. Über der Muscularis mucosae sind die Lymphozyten in unscharf begrenzten Haufen angesammelt.

Zusammenfassung. Im Pylorus deutliche entzündliche Veränderungen, stellenweise leichte Veränderungen in der Gruppierung der Drüsen, keine Atrophien.

Im Fundus hochgradige entzündliche Veränderungen, mässige Drüsenatrophie, die Deckzellen erhalten.

Duodenum. Die Drüsengruppen in den Brunnerschen Drüsen gut entwickelt, spärlich Lymphozyten und Plasmazellen zwischen den Acini.

Fall 4. 62jähriger Geschäftsführer, aufgenommen 26. 3. 1914, gestorben 4. 4. 1914. *Klinische Diagnose:* *Anaemia perniciosa*. Arteriosclerosis. 30. 3. 1914. Hb 16. Die Sektion, 3 Stunden nach dem Tode, bestätigt die klinische Diagnose. Aus dem Sektionsprotokoll: Im Magen, in der Nähe des Pylorus, wird ein kleinfingerendgrosser Polyp angetroffen. Im übrigen ist die Schleimhaut glatt, im Fundus einige kleine Blutungen.

Pylorus. Das Oberflächenepithel ist nur stellenweise erhalten. Lieberkühnsche Darmkrypten sind an mehreren Stellen des Präparats zu sehen. Die Pylorusdrüsen treten unregelmässig in der Schleimhaut auf. An manchen Stellen fehlen sie ganz und sind durch nicht zu feinfaseriges Bindegewebe ersetzt. Die Foveolae gastricae und die Drüsen haben hier und da einen geschlängelten Verlauf. Über der Muscularis mucosae sind die Drüsengänge mancherorts zu kleinen, gut abgegrenzten Gruppen gesammelt. Die Drüsenlumina zeigen variierende Grösse. Die Zellen sind dunkel, nicht sekretgefüllt. Lymphozyten und Plasmazellen sind überall, besonders in der oberen Hälfte der Schleimhaut, reichlich zu finden. Auch Russellsche Körperchen sieht man in den oberen Schichten reichlich.

Fundus. Oberflächenepithel abgestossen. Zahlreiche Darmkrypten in dem Präparat. Kleine Drüsenkonglomerate treten weit zerstreut in der dünnen Tunica propria auf. Die Drüsengänge sind kurz, verkümmert und aus hellen oder dunkelgefärbten Zellen aufgebaut. Keine Deckzellen. Bindegewebe feinfaserig. Überall sind reichlich Lymphozyten und Plasmazellen, spärlich neutrophile Granulozyten zu sehen.

Zusammenfassung. Sowohl im Pylorus als im Fundus deutliche entzündliche Veränderungen, Drüsenatrophie und Umbau der Drüsen. Die Atrophie ist hochgradiger im Fundus, aber auch im Pylorus ausgeprägt.

Duodenum. Brunnersche Drüsengruppen wohlentwickelt. Zellen hell, zwischen den Acini spärlich Lymphozyten und Plasmazellen. In manchen Drüsengruppen findet man Bindegewebe zwischen den Drüsengängen in etwas vermehrter Menge.

Fall 5. 36jährige Frau, aufgenommen 16. 2. 1914, gestorben 13. 4. 1914. *Klinische Diagnose:* *Anaemia perniciosa*. 6. 4. 1914. Hb 21. Die Sektion, 4 Stunden nach dem Tode, bestätigt die klinische Diagnose.

Pylorus. Das Oberflächenepithel ist nur stellenweise erhalten, die Zellen sind in auffallendem Grade sekretgefüllt. Die Foveolae gastricae nehmen hier und da $\frac{3}{4}$ der Tunica propria ein. Die Pylorusdrüsen sind in reicher Menge vorhanden, zeigen aber nur an manchen Stellen ein normales Aussehen. Sie haben einen geschlängelten Verlauf, das Kaliber wechselt mancherorts in hohem Grade, das Lumen ist in manchen Drüsengängen vergrössert und die Zellen abgeplattet. Lieberkühnsche Darmkrypten sind spärlich anzutreffen. Entzündungszellen, vor allem Lympho-

zyten und Plasmazellen, sind überall in reicher Menge zu sehen. An manchen Stellen enthalten die erweiterten Drüsengänge neutrophile Granulozyten.

Fundus. Das Oberflächenepithel ist nur stellenweise erhalten, die Zellen bieten nichts Abnormes. Die Foveolae gastricae nehmen mehr als die Hälfte der Tunica propria ein. Die Drüsen sind klein und verkümmert, treten aber in ziemlich reicher Menge auf. Die Drüsengänge sind aus dunklen abgeplatteten Zellen mit basal gestellten ovalen Kernen oder aus hohen, hellen, sekretgefüllten Zellen aufgebaut. Keine Deckzellen. Die Drüsengänge sind stellenweise in Gruppen gesammelt, zwischen denen mit Haufen von Lymphozyten ausgefüllte Lücken zu sehen sind. Man bemerkt mehrere Darmkrypten. Entzündungszellen in Form von Lymphozyten und Plasmazellen erscheinen überall in reicher Menge in der Tunica propria, stellenweise auch in der Muscularis mucosae und in den obersten Schichten der Submucosa. Auch neutrophilen und einzelnen eosinophilen Granulozyten begegnet man.

Zusammenfassung. Im Pylorus und Fundus hochgradige entzündliche Veränderungen, mässige Drüsenatrophie, aber verändertes Aussehen der Drüsen sowohl im Fundus als im Pylorus. Die Atrophie im Fundus etwas ausgeprägter als im Pylorus.

Duodenum. In manchen Brunnerschen Drüsengruppen spärlich Plasmazellen und Lymphozyten.

Fall 6. 36jährige Zimmermannsfrau, aufgenommen 15. 11. 1914, gestorben 14. 3. 1915. *Klinische Diagnose:* *Anaemia perniciosa.* 12. 3. 1915. Hb. 47. Bei der Sektion, 2 ½ Stunden nach dem Tode, wird eine Gehirnblutung im linken Linsenkern konstatiert; im übrigen wird die klinische Diagnose bestätigt.

Pylorus. Das Oberflächenepithel ist überall erhalten, in den Zellen bemerkt man reichlich Sekret. Die Foveolae gastricae nehmen 2/3 der Tunica propria ein. Die Pylorusdrüsen sind kurz und geschlängelt und treten in unscharf abgegrenzten Gruppen geordnet auf. Sie fehlen stellenweise gänzlich. Nur manche Drüsenzellen sind sekretführend und hell. Die meisten sind dunkel. Das Präparat weist einige Darmkrypten auf. Zahlreiche Russellsche Körperchen in der obersten Schicht der Schleimhaut. Überall in der Tunica propria, stellenweise auch in der Muscularis mucosae und der obersten Schicht der Submucosa, reichlich Lymphozyten und Plasmazellen sowie recht zahlreich auch eosinophile Granulozyten.

Fundus. Das Oberflächenepithel ist zum grossen Teil bewahrt. Die Drüsen liegen ziemlich weit auseinander. Sie sind kurz und geschlängelt und stellenweise zu undeutlich abgegrenzten Gruppen gesammelt. Die Drüsengänge, deren Kaliber etwas variiert, sind aus dunklen zylinderförmigen Zellen aufgebaut. Deckzellen fehlen. Entzündungszellen, zu meist Plasmazellen und Lymphozyten, sind überall in der Tunica propria, stellenweise auch in der Muscularis mucosae und in der obersten Schicht der Submucosa zu sehen. Zahlreiche Russellsche Körperchen.

Zusammenfassung. Hochgradige entzündliche Veränderungen im Pylorus und Fundus sowie mässige Atrophie und Umbau der Drüsen. Die Atrophie im Fundusteil etwas ausgeprägter.

Duodenum. Spärlich Lymphozyten und Plasmazellen zwischen den Drüsenacini in den Brunnerschen Drüsen. Die Drüsenzellen sind sekretgefüllt und weisen nichts Abnormes auf.

Fall 7. 63jährige Steinarbeiterfrau, aufgenommen 12. 3. 1915, gestorben 16. 3. 1915. *Klinische Diagnose:* Anaemia perniciosa. Stenosis intestini. Nephritis chron. Degeneratio amyloidea. Bronchitis chron. Bronchopneumonia. 15. 3. 1915. Hb 39. Sektion 5 ½ Stunden nach dem Tode. Aus dem Sektionsprotokoll: Lobäre Pneumonie in der linken Lunge. Amyloidentartung in der Milz, den Nieren, der Leber und den Därmen. Magen fast leer. Schleimhaut glatt, mit einigen kleinen Blutungen. Fibröse Adhärenzen zwischen den beiden Schenkeln der Flexura lienalis und um den unteren Teil des Colon descendens.

Pylorus. Das Oberflächenepithel ist abgestossen. Die Drüsen sind lang, verzweigt und liegen weiter auseinander als normal sowie in Gruppen angeordnet. Zystenähnliche erweiterte Drüsengänge sind stellenweise zu sehen. Die Drüsenzellen sind dunkel, zylindrisch oder in manchen Drüsengängen hell, mit basal gestellten, abgeplatteten Kernen. Entzündungszellen finden sich überall zwischen den Drüsen und bestehen hauptsächlich in Lymphozyten und Plasmazellen. Eosinophile und neutrophile Granulozyten kommen spärlich vor.

Fundus. Recht hochgradige kadaveröse Veränderungen. Die Drüsen weit auseinanderliegend, gruppenweise auftretend. Keine Deckzellen. Zahlreiche Entzündungszellen.

Zusammenfassung. Hochgradige entzündliche Veränderungen im Pylorus und Fundus. Hochgradige Drüsenatrophie im Fundus, aber auch im Pylorus, obwohl hier weniger ausgeprägt. Umbau der Drüsen sowohl im Pylorus als im Fundus.

Duodenum. Die Brunnerschen Drüsen treten in kleinen Gruppen auf und lassen nichts Abnormes erkennen.

Fall 8. 34jährige Lokomotivführersfrau, aufgenommen 10. 4. 1915, gestorben 14. 7. 1915. *Klinische Diagnose:* Anaemia perniciosa. 13. 7. 1915. Hb 8. Eine Stunde nach dem Tode wurde 500 cm³ Formaldehydlösung in die Bauchhöhle eingespritzt. Die Sektion, 3 ½ Stunden nach dem Tode, bestätigt die klinische Diagnose. Aus dem Sektionsprotokoll: Im Magen unbedeutend rotbraune Flüssigkeit, die Schleimhaut glatt, anscheinend etwas atrophisch. Magenwand dünn.

Pylorus. Das Oberflächenepithel ist überall wohl erhalten, die Zellen enthalten reichlich Sekret. Foveolae gastricae und Pylorusdrüsen geschlängelt. Die letzteren treten gruppenweise auf und liegen oft ziemlich weit auseinander. Drüsenzellen hell, feingranuliert. Drüsenlumina mancherorts erweitert. Von der Muscularis mucosae strahlt nicht zu feinfaseriges Bindegewebe zwischen die Drüsengruppen aufwärts. Überall im interstitiellen Gewebe zeigen sich zahlreiche Lymphoidzellen. Neutro-

phile und eosinophile Granulozyten treten ausserdem in nicht allzu spärlicher Menge auf. Russellsche Körperchen kommen spärlich vor. Kein Darmepithel.

Fundus. Oberflächenepithel nur stellenweise erhalten; in den Zellen reichlich Sekret. Die Drüsen sind klein und verkümmert und treten hier und da in dichten Gruppen auf. Zellen dunkel oder mit einem hellen Sekret gefüllt. Keine Deckzellen. Zahlreiche Entzündungszellen überall in der Schleimhaut, zumeist Lymphoidzellen, in geringerer Menge eosinophile und neutrophile Granulozyten.

Zusammenfassung. Hochgradige entzündliche Veränderungen im Pylorus und Fundus. Hochgradige Drüsenatrophie im Fundus, etwas weniger hochgradige im Pylorus.

Duodenum. Brunnersche Drüsen sind nicht festzustellen.

Fall 9. 50jährige Arbeiterfrau, aufgenommen 9. 2. 1915, gestorben 26. 10. 1915. *Klinische Diagnose:* *Anaemia perniciosa*. 19. 10. 1915. Hb 25. Eine halbe Stunde nach dem Tode wurde 500 cm³ Formaldehydlösung in die Bauchhöhle eingespritzt. Die Sektion, 5 Stunden nach dem Tode, bestätigt die klinische Diagnose.

Pylorus. Oberflächenepithel wohlerhalten. In den Zellen reichlich Sekret. Foveolae gastricae geschlängelt, stellenweise mit einer gelblichen Masse gefüllt. Die Pylorusdrüsen sind in Gruppen gesammelt, die Drüsengänge haben einen unregelmässigen Verlauf und zeigen wechselndes Kaliber, die Zellen sind hell, sekretgefüllt. Von der Muscularis mucosae strahlt nicht allzu feinfaseriges Bindegewebe zwischen den Drüsengruppen aufwärts. In der Tunica propria und auch im obersten Teil der Submucosa sieht man ziemlich reichlich Plasmazellen und Lymphozyten. Die letzteren treten oft in dichten, unscharf begrenzten Gruppen hier und da, hauptsächlich in den basalen Teilen der Tunica propria auf. Russellsche Körperchen kommen vor, aber ziemlich spärlich.

Fundus. Oberflächenepithel erhalten. Die Schleimhaut ist etwas ausgedehnt. Die Drüsen sind kurz und bilden Gruppen dichtgestellter, unregelmässig verlaufender, quergeschnittener Drüsengänge. Zwischen den Gruppen mit feinfaserigem interstitiellen Bindegewebe ausgefüllte Lücken. In den Drüsen sind die Lumina oft etwas erweitert und bestehen aus dunklen kubischen oder abgeplatteten Zellen. Keine Deckzellen. Zahlreiche Russellsche Körperchen. Lymphozyten und Plasmazellen sowie auch neutrophile und eosinophile Granulozyten sind überall in den Drüseninterstitien zu sehen.

Zusammenfassung. Hochgradige entzündliche Veränderungen im Fundus und Pylorus. Ziemlich hochgradige Atrophie und Umbau der Drüsen im Fundus, aber auch, obwohl in geringerem Grade, im Pylorus.

Duodenum. In den Brunnerschen Drüsen ist nichts Abnormes festzustellen.

Fall 10. 61jährige Witwe, aufgenommen 3. 4. 1916, gestorben 14. 4. 1916. *Klinische Diagnose:* *Anaemia perniciosa*. Lues. Alcoholismus

chron. 12. 4. 1916. Hb 19. Die Sektion, 10 Stunden nach dem Tode, bestätigt die Diagnose *Anaemia perniciosa*.

Pylorus. Hochgradige postmortale Veränderungen. Aus der Untersuchung geht hervor, dass sich die Drüsen zu ziemlich lichtgestellten Konglomeraten ungruppiert haben, in denen die einzelnen Drüsengänge kurz und geschlängelt sind. Überall in der Tunica propria sieht man eine dichte Infiltration von Lymphoidzellen.

Zusammenfassung. Hochgradige entzündliche Veränderungen. Mässige Atrophie und Umbau der Drüsen.

Duodenum. Die Brunnerschen Drüsen weisen nichts Abnormes auf.

Fall 11. 78jährige Landwirtswitwe, aufgenommen 2. 4. 1916, gestorben 8. 7. 1916. *Klinische Diagnose: Anaemia perniciosa*. Arteriosclerosis, Cholelithiasis. 4. 7. 1916. Hb 31. Die Sektion, eine Stunde nach dem Tode, bestätigt die klinische Diagnose. Auszug aus dem Sektionsprotokoll: In der Magenschleimhaut, die ziemlich glatt ist, sieht man zerstreute kleine Blutungen.

Pylorus. Das Oberflächenepithel ist erhalten, die Zellen zeigen nichts Abnormes. Stellenweise Darmepithel mit Panetschen Zellen in den Krypten. Die Pylorusdrüsen zu dichten Konglomeraten über der Muscularis mucosae zusammengefasst. Drüsenzellen hell, hoch, sekretgefüllt, mit abgeplatteten, basalgestellten Kernen. An manchen Stellen fehlen die Pylorusdrüsen gänzlich, und zwischen den Drüsengruppen tritt ziemlich grobfaseriges Bindegewebe in deutlich vermehrter Menge auf. Überall in dem interstitiellen Gewebe sind zahlreiche Lymphozyten und Plasmazellen zusehen. Mehrerorts finden sich Lymphozyten in grossen, dichten, unscharf begrenzten Haufen. Nur spärlich sind eosinophile und neutrophile Granulozyten anzutreffen. Russellsche Körperchen kommen zahlreich vor.

Fundus. Oberflächenepithel abgestossen. In der Schleimhaut findet man zahlreiche Lieberkühnsche Darmkrypten und zwischen diesen helle Drüsenkonglomerate, die in hohem Grade an die Drüsen im Präparat aus dem Pylorus erinnern. Von den Drüsenzellen sind die meisten hoch, hell, sekretgefüllt, mit zusammengedrückten Zellkernen in der Zellbasis, die übrigen zylindrisch, dunkler gefärbt, mit abgerundeten Kernen, keine Deckzellen. Zahlreiche Russellsche Körperchen. Reichlich Lymphozyten und Plasmazellen, spärlich eosinophile und neutrophile Granulozyten in der Tunica propria.

Zusammenfassung. Hochgradige entzündliche Veränderungen im Pylorus und Fundus. Ein Umbau der Drüsen und Zeichen einer Atrophie treten in beiden Magenabschnitten auf, die histologisch einander stark ähneln. Die Atrophie, die als mässig zu bezeichnen ist, ist im Fundus vielleicht etwas deutlicher als im Pylorus.

Duodenum. Brunnersche Drüsen sind nur spärlich zu bemerken. Sie zeigen nichts Abnormes.

Fall 12. 57jährige Kellnerin, aufgenommen 10. 7. 1916, gestorben 12. 8. 1916. *Klinische Diagnose: Anaemia perniciosa*. Accessit: Parotitis acuta. Bronchopneumonia. 10. 8. 1916. Hb 20. Die Sektion, 2 ½ Stunden

nach dem Tode, bestätigt die Diagnose Anaemia perniciosa. Aus dem Sektionsprotokoll: Die Magenschleimhaut erscheint dünn und enthält zahlreiche Ekchymosen.

Pylorus. Das Oberflächenepithel ist nur stellenweise erhalten. Drüsen finden sich ziemlich reichlich. In der Drüsenanordnung kann eine gewisse Abnormität festgestellt werden. Der Abstand zwischen den Drüsen ist mehrerorts vergrößert. Die Drüsengänge sind in ihrem basalen Teil geschlängelt, und die quergeschnittenen Gänge lassen eine Andeutung von Gruppenbildung erkennen. Sowohl in den Foveolae gastricae als in sämtlichen Drüsen haben die Zellen das gleiche Aussehen und unterscheiden sich deutlich von den entsprechenden Zellen in den Kontrollpräparaten. Die Zellform ist ziemlich kubisch, das Plasma gleichmässig braun und feingranuliert, der Kern abgerundet und in der basalen Hälfte der Zelle gelegen. Überall konstatiert man eine diffuse Infiltration mit Lymphozyten und Plasmazellen. Neutrophile und eosinophile Granulozyten kommen spärlich vor.

Fundus. Oberflächenepithel abgestossen. Die Schleimhaut erinnert in hohem Grade an die Schleimhaut aus dem Pylorus. Die Drüsen haben ungefähr das gleiche Aussehen. Sie sind kurz, geschlängelt, treten in ziemlich weit auseinanderliegenden Gruppen auf und sind aus ähnlichen kubischen, etwas basophilen Zellen wie im Pylorusteil aufgebaut. Keine Deckzellen. Entzündungszellen finden sich reichlich in der Muscularis mucosae. Sie bestehen in Lymphoidzellen und eosinophilen und neutrophilen Granulozyten.

Zusammenfassung. Pylorus und Fundus erinnern stark aneinander. Ausgeprägte entzündliche Veränderungen sind in beiden Magenabschnitten zu sehen. Die Drüsen haben an beiden Stellen dasselbe abnorme Aussehen, aber die Atrophie ist im Fundus ausgeprägter, im Pylorus weniger hochgradig.

Duodenum. In dem untersuchten Präparat keine Brunnerschen Drüsen.

Fall 13. 41jährige Haushälterin, aufgenommen 7. 9. 1916, gestorben 22. 9. 1916. *Klinische Diagnose:* Anaemia perniciosa. Nephrosclerosis. Hypertrophia et dilatatio cordis. 21. 9. 1916. Hb 13. Die Sektion, eine Stunde nach dem Tode, bestätigt die klinische Diagnose. Aus dem Sektionsprotokoll: Magenschleimhaut blass.

Pylorus. Oberflächenepithel zum grossen Teil erhalten, die Zellen hochgradig sekretgefüllt. Die Drüsen erscheinen ziemlich gleichmässig in der Schleimhaut verteilt. Die Zwischenräume zwischen ihnen sind jedoch breiter als in den Kontrollfällen. Die Drüsengänge haben wechselndes Kaliber. Manche sind klein, verkümmert, andere gross, mit erweitertem Lumen und hellen sekretgefüllten Zellen. In dem feinfaserigen interstitiellen Gewebe sind Plasmazellen und Lymphozyten sowie zahlreiche eosinophile und neutrophile Leukozyten zu sehen.

Zusammenfassung. Deutliche entzündliche Veränderungen in der Schleimhaut. Mässige Drüsenatrophie und Umbau der Drüsen.

Duodenum. Keine Brunnerschen Drüsen.

Fall 14. 31jähriger Landwirt, aufgenommen 21. 1. 1917, gestorben 15. 2. 1917. *Klinische Diagnose: Anaemia perniciosa.* 7. 2. 1917. Hb 21. Die Sektion, 2 Stunden nach dem Tode, bestätigt die klinische Diagnose.

Pylorus. Das Oberflächenepithel ist überall erhalten, die Zellen weisen nichts Abnormes auf. Die Foveolae gastricae sind zu langen Röhren ausgezogen, die 2/3 der Tunica propria einnehmen. Pylorusdrüsen kommen in reicher Menge vor. Drüsenzellen hell, granuliert, mehrerorts sekretgefüllt. Stellenweise ist das Bindegewebe zwischen den Drüsen jedoch vermehrt und steigt von der Tunica propria zur Oberfläche hinauf, und an entsprechenden Stellen kann man Verschiebungen in der Gruppierung der Drüsen konstatieren. Lymphozyten und Plasmazellen sind reichlich in der oberen Hälfte der Schleimhaut, aber auch in dem Bindegewebe über der Muscularis mucosae zu sehen. Neutrophile Granulozyten sind hauptsächlich in und unter dem Oberflächenepithel anzutreffen.

Fundus. Das Oberflächenepithel ist ziemlich gut erhalten, die Zellen bieten nichts Abnormes dar. Die Foveolae gastricae sind lang und schmal und umfassen stellenweise 2/3 der Tunica propria. Die Drüsen haben dasselbe Aussehen wie im Pylorus, Deckzellen fehlen. Die Drüsengänge sind ziemlich kurz und geschlängelt, finden sich aber in reicher Menge. Man sieht jedoch zwischen ihnen stellenweise Lücken, die mit feinfaserigem interstitiellen Gewebe angefüllt sind. Zwischen den Drüsen zahlreiche Entzündungszellen, zumeist Lymphozyten und Plasmazellen, in geringerer Menge auch neutrophile Granulozyten.

Zusammenfassung. Deutliche entzündliche Veränderungen sowohl im Fundus als im Pylorus. Umwandlung der Drüsen im Fundus. Beginnende Umgruppierung der Drüsen. Keine ausgeprägte Drüsenatrophie.

Fall 15. 19jähriger Handlungsgehilfe, aufgenommen 23. 1. 1914, gestorben 3. 4. 1914. *Klinische Diagnose: Anaemia perniciosa.* Bothriocephalus latus. 2. 2. 1914. Hb 14. Die Sektion, 13 Stunden nach dem Tode, bestätigt die klinische Diagnose. Aus dem Sektionsprotokoll: Magenschleimhaut blass und glatt. Im oberen Teil des Ileums ein 20 cm langes Stück Bothriocephalus latus.

Pylorus. Oberflächenepithel abgestossen. Pylorusdrüsen lang und dichtgestellt. Lymphoidzellen treten überall zahlreich auf. Die Lymphozyten sind stellenweise in kleinen, unscharf begrenzten Haufen über der Muscularis mucosae gesammelt.

Fundus. Hochgradige kadaveröse Veränderungen. Es ergibt sich jedoch, dass die Tunica propria sich aus langen, dichtliegenden Drüsengängen aufbaute, die mit Deckzellen versehen waren. Entzündungszellen finden sich in erhöhter Menge, besonders in der obersten Schicht der Schleimhaut.

Zusammenfassung. Sowohl im Fundus als im Pylorus entzündliche Veränderungen. Keine Zeichen von Drüsenatrophie. Deckzellen in den Fundusdrüsen.

Duodenum. Die Zellen in den Brunnerschen Drüsen dunkel. Keine Zeichen einer Entzündung.

Fall 16. 65jähriger Arbeiter, aufgenommen 24. 2. 1914, gestorben 26. 2. 1914. *Klinische Diagnose:* *Anaemia perniciosa*. *Bothriocephalus latus*. Arteriosclerosis. Alcoholismus. Hb 21. Die Sektion, 4 Stunden nach dem Tode, bestätigt die klinische Diagnose. Aus dem Sektionsprotokoll: Magenschleimhaut glatt, gerötet, nicht besonders dünn. Im Darminhalt sind im unteren Teil des Dickdarms zahlreiche *Bothriocephalus*-eier anzutreffen.

Pylorus. Schleimhaut dünn, etwa $\frac{1}{2}$ der Norm. Die Dicke der Muskelschicht deutet darauf hin, dass die Schleimhaut nicht dilatiert ist. Das Oberflächenepithel ist überall bewahrt, in den Zellen reichlich Sekret. Die Drüsen sind weitläufig gestellt. Sie sind auffallend kurz, mit erweitertem Lumen und haben einen unregelmässigen Verlauf. Die Drüsenzellen zeigen kubische Form. In manchen Drüsen sind sie hell, in anderen haben sie etwas Farbe angenommen. In den hellen Zellen sind die Kerne basal gestellt und abgeplattet, in den dunklen zentral gelegen und abgerundet. Helle und dunkle Zellen kommen im Querschnitt ein und desselben Ganges vor, und man sieht alle Zwischenformen von ihnen. Deckzellen sind ziemlich spärlich und nicht in allen Drüsen anzutreffen. Darmepithel ist nicht vorhanden. Die Drüsengänge sind geschlängelt und treten in kleinen Gruppen angeordnet im Schnitt auf. Zwischen den Gruppen findet man ein lockeres feinfaseriges Bindegewebe und in diesem Entzündungszellen in reicher Menge. Die letzteren sind hauptsächlich Lymphozyten und Plasmazellen. Eosinophile und neutrophile Granulozyten kommen auch in nicht allzu spärlicher Menge vor. Über der Muscularis mucosae bilden die Lymphozyten an mehreren Stellen unscharf begrenzte Infiltrate. In dem Bindegewebe sieht man im ganzen Präparat, besonders in den oberen Teilen der Schleimhaut, Russellsche Körperchen und zerfallende rote Blutkörperchen.

Fundus. Das Oberflächenepithel fehlt. Drüsen weit auseinanderliegend, kurz, mit unregelmässigem Verlauf und erweitertem Lumen. Die Drüsenzellen bestehen in indifferenten, kubischen oder mit dunklem Plasma versehenen Zellen. Spärlich Deckzellen in den Drüsengängen. Zahlreiche Entzündungszellen derselben Art wie im Pylorus.

Zusammenfassung. Hochgradige entzündliche Veränderungen mit weit fortgeschrittener Drüsenatrophie und Umbau der Drüsen sowohl im Fundus als im Pylorus. Die Atrophie in beiden Präparaten gleich ausgeprägt. Deckzellen sind anzutreffen.

Duodenum. Drüsengewebe reichlich vorhanden. Drüsenzellen hell. Die Kerne basal gestellt, abgeplattet. Drüsenlumina klein. Bindegewebe zwischen den Drüsenacini nicht vermehrt, enthält stellenweise Lymphozyten und Plasmazellen.

Fall 17. 58jährige Arbeiterin, aufgenommen 29. 3. 1943, gestorben 30. 3. 1943. *Klinische Diagnose:* *Anaemia perniciosa*. 30. 3. 1943. Hb 16/19. Die Patientin ist nicht mit Leber- oder Magenpräparaten behandelt worden. Die Sektion, 10 Stunden nach dem Tode, bestätigt die klinische Diagnose.

Pylorus. Oberflächenepithel abgestossen. Zwischen den Drüsen, die in reicher Menge vorhanden sind, sieht man mehrerorts drüsenfreie Lücken. Die Drüsengänge sind kürzer als normal, geschlängelt und an manchen Stellen in Gruppen gesammelt. Sie sind teils klein, verkümmert und aus dunklen Zellen aufgebaut, teils gross, mit hellen sekretgefüllten Zellen. Darmkrypten sind zahlreich unter den Pylorusdrüsen eingestreut. Entzündungszellen finden sich überall in den Interstitien. Sie bestehen hauptsächlich in Lymphozyten und Plasmazellen. Russellsche Körperchen kommen recht zahlreich vor.

Fundus. Das Oberflächenepithel ist abgestossen. Die Schleimhaut erinnert in hohem Grade an diejenige im Pylorus. Die Drüsengänge sind vom gleichen Aussehen und bestehen teils aus kleinen, dunklen, teils aus grossen, hellen und sekretgefüllten Zellen. Keine Deckzellen. Die Drüsen sind in etwas undeutlich begrenzten Gruppen gesammelt, zwischen denen drüsenfreie Lücken auftreten. Entzündungszellen finden sich reichlich in dem interstitiellen Teil. Mehrere Darmkrypten sind anzutreffen.

Zusammenfassung. Pylorus und Fundus von gleichem Aussehen. Deutliche entzündliche Veränderungen. Mässige Atrophie der Drüsen. Umbau der Drüsen.

Duodenum. Die Brunnerschen Drüsen, die in reicher Menge vorhanden sind, zeigen nichts Abnormes.

Fall 18. 63jähriger ehem. Diener, seit 1929 wiederholt im Krankenhaus. Zuletzt aufgenommen 12. 2. 1943, gestorben 2. 3. 1943. *Klinische Diagnose:* *Anaemia perniciosa.* Arteriosclerosis. Myodegeneratio cordis. Hypertonia. Encephalomalacia. Diabetés mellitus.

Der Patient ist mehrere Jahre wegen seiner Anämie behandelt worden, ist aber zeitweise mit kleinen Mengen antianämischer Organpräparate zurechtgekommen. Bekam seine letzte »Leberinjektion« im September 1942. Blutprobe am 15. 2. 1943: Hb 83/96, E: 4,880,000, I: 0.98, L: 8,800. Sektion 8 ½ Stunden nach dem Tode. Obduktionsdiagnose: Hypertrophia cordis. Nephrosclerosis benigna. Hydrothorax l. d. (Das Cranium wurde nicht geöffnet.)

Pylorus. Oberflächenepithel abgestossen. Die Pylorusdrüsen sind lang und wohlentwickelt, mit hellen sekretgefüllten Zellen. Die Drüsen treten ungefähr ebenso dicht wie in den Kontrollfällen auf. In den Drüseninterstitien sind überall ziemlich reichlich Lymphozyten und Plasmazellen zu sehen.

Fundus. In der Schleimhaut hochgradige kadaveröse Veränderungen. Der Fundus kann daher nicht näher untersucht werden.

Zusammenfassung. Im Pylorus deutliche Zeichen einer Entzündung. Keine Zeichen von Atrophie oder Umbau des Drüsenapparats.

Duodenum. Die Brunnerschen Drüsen zeigen in ihrem Bau nichts Abnormes, sind aber in auffallend kleinen Mengen anzutreffen.

Zusammenstellung der mikroskopischen Befunde.

Pylorusteil.

In sämtlichen 18 Fällen wurden Entzündungszellen in erhöhter Menge im interstitiellen Gewebe der Tunica propria festgestellt. Die Zellen sind hauptsächlich Lymphozyten und Plasmazellen. Auch eosinophile und neutrophile Granulozyten werden oft, wenn auch in geringerer Menge, angetroffen. Russellsche Körperchen finden sich nicht selten in grosser Zahl in der Schleimhaut.

Die Drüsen zeigen meist nicht dasselbe Aussehen wie in den normalen Kontrollfällen (Abb. 1), sondern lassen in ihrem Verlauf und ihrer Anordnung Unregelmässigkeiten erkennen, wie sie aus Abb. 2—7 ersichtlich werden. Die Drüsengänge sind verästelt, mit kürzeren Endverzweigungen als normalerweise und treten zu Trauben oder Drüsengruppen gesammelt auf. Eine solche gruppenförmige Anordnung der Drüsen wurde mehr oder weniger deutlich in 12 der untersuchten Fälle (1, 2, 4, 6, 7, 8, 9, 10, 11, 12, 16, 17) beobachtet. Aus den Präparaten geht hervor, dass die Gruppen nicht durch die Schnittführung bedingt sind. Die Drüsengänge können kürzer als normal sein (6, 10, 13, 16, 17). Das Lumen ist manchmal erweitert (5, 7, 8, 13), und die Drüsen erscheinen in geringerer Zahl und in weiteren Abständen voneinander als normal (Abb. 3, 5, 6). Derartige atrophische Veränderungen sind in 4 Fällen (2, 4, 7, 16) als hochgradig und in 10 Fällen (1, 5, 6, 8, 9, 10, 11, 12, 13, 17) als mässig oder leicht bezeichnet worden. Nur in 4 Fällen (3, 14, 15, 18) waren keine Zeichen von Atrophie zu bemerken. Im Oberflächenepithel enthalten die Zellen in 7 Fällen (3, 5, 6, 8, 9, 13, 16) auffallend reichlich Sekret (Abb. 8), und die Foveolae sind in 4 Fällen (3, 5, 6, 14) abnorm lang. Darmepithel ist in 6 Fällen (2, 4, 5, 6, 11, 17) anzutreffen (siehe Abb. 3, 4, 5).

Fundusteil.

In allen Fällen sind in der Tunica propria Entzündungszellen in erhöhter Menge zu beobachten. Diese Zellen sind hauptsächlich Lymphozyten und Plasmazellen. Oft waren auch eosinophile und neutrophile Granulozyten zu bemerken. Russellsche Körperchen kommen vor, aber nicht so oft und so reichlich wie im Pylorusteil.

Atrophische Veränderungen der Schleimhaut treten in den



Abb. 1. Normale Pylorusdrüsen.

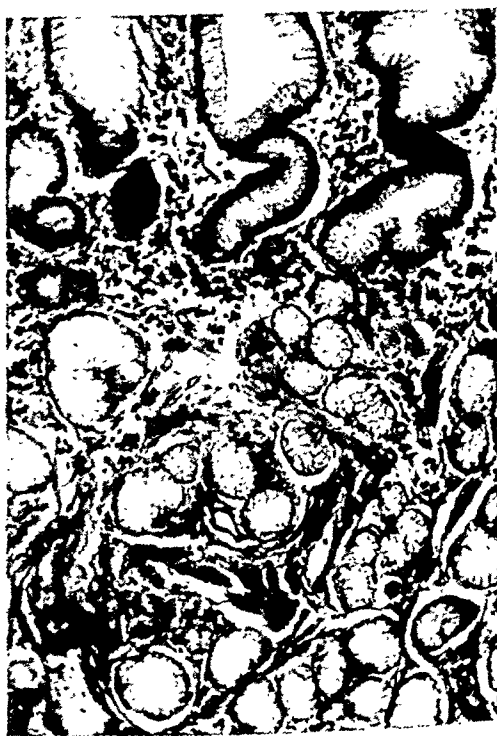


Abb. 2. Pylorusschleimhaut aus Fall 9. Der Verlauf der Drüsen ist unregelmässig. Der untere Teil der Foveolae gastricae geschlängelt.



Abb. 3. Pylorusschleimhaut aus Fall 11. Die Pylorusdrüsen sind zu hellen, von grossen atrophischen Partien umgebenen Trauben angeordnet. Der lange Gang in der Mitte der Abbildung ist von Darmepithel mit hellen Becherzellen ausgekleidet. Entzündungszellen finden sich zahlreich im oberen Teil der Schleimhaut.

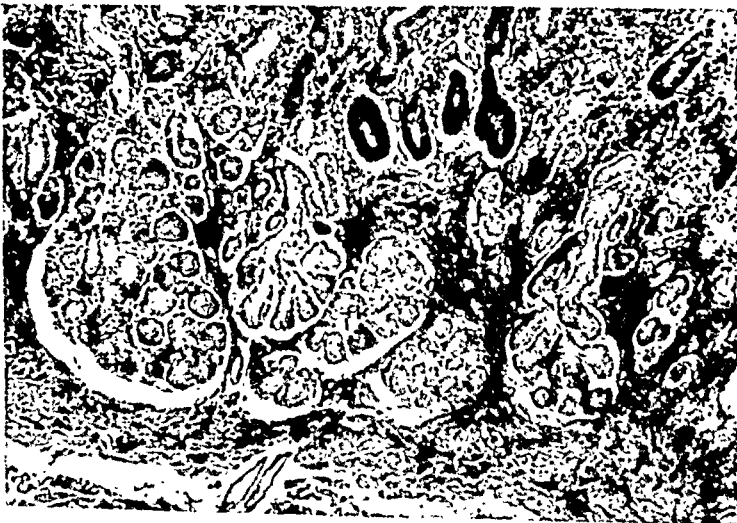


Abb. 4. Pylorusschleimhaut aus Fall 4. Die Drüsen sind zu Trauben angeordnet. Die dunklen Drüsen sind Darmkrypten. Reichlich Entzündungszellen in dem interstitiellen Gewebe.

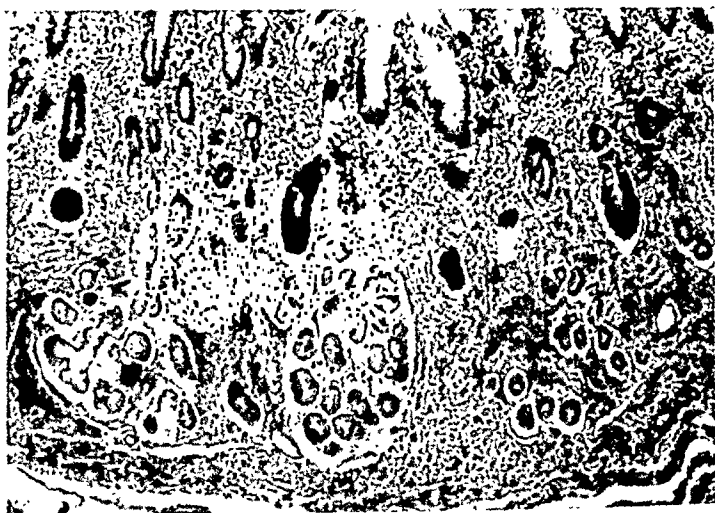


Abb. 5. Pylorusschleimhaut aus Fall 4. Die Drüsen in Gruppen angeordnet. Grosse atrophische Gebiete. Mehrere dunkle Darmkrypten sind in dem Präparat zu erkennen.



Abb. 6. Pylorusschleimhaut aus Fall 8. Die Drüsen unregelmässig verteilt, deutliche Atrophie. Reichlich Entzündungszellen in dem interstitiellen Gewebe zwischen den Drüsengruppen.

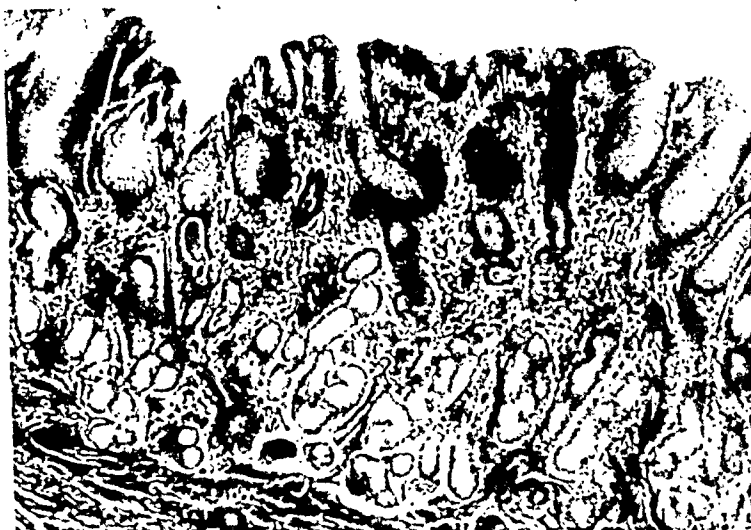


Abb. 7. Pylorusschleimhaut aus Fall 9. Drüsen kommen in ziemlich reicher Menge vor, haben aber einen unregelmässigen Verlauf und eine abnorme Anordnung. Foveolae gastricae geschlängelt und sekretgefüllt. Zahlreiche Entzündungszellen in dem interstitiellen Gewebe.

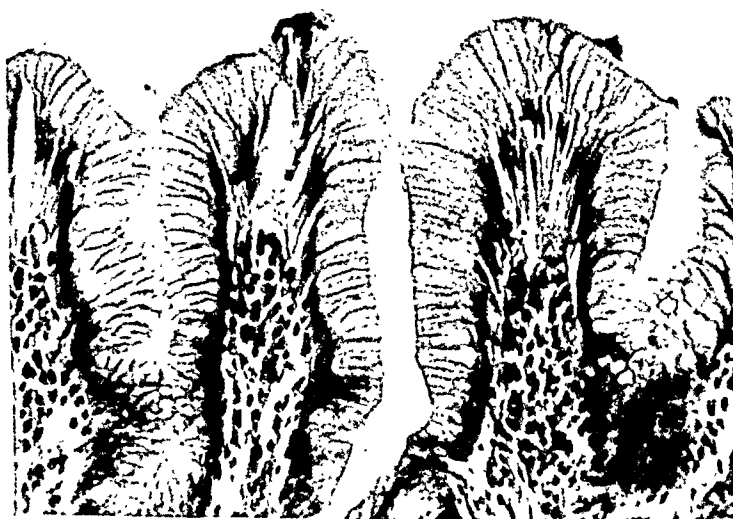


Abb. 8. Oberflächenepithel aus dem Pylorusteil in Fall 8. Die Zellen enthalten Sekret in abnorm reicher Menge.

meisten Fällen auf. Sie können in 8 Fällen (1, 2, 4, 7, 8, 9, 11, 16) als hochgradig und in 4 Fällen (5, 6, 12, 17) als mässig bezeichnet werden. Die Atrophie hat jedoch nie zu vollständiger Anadenie geführt. Keine Atrophie war in 3 Fällen (14, 15, 18) zu finden. (In 3 Fällen wurde nur der Pylorusteil untersucht.) Die Drüsen sind aus indifferenten Zellen aufgebaut. Deckzellen kommen nur in 3 Fällen (3, 15, 16) vor, aber in spärlicher Menge. Die Drüsen sind mitunter erweitert (3, 9, 16). Auch im Fundus treten die Drüsen oft gruppenweise auf (5, 6, 7, 8, 9, 11, 12, 17) und sind in den meisten Fällen verkümmert (1, 2, 3, 4, 5, 6, 8, 9, 12, 14, 16, 17). Darmepithel sieht man in 5 der Fälle (1, 4, 5, 11, 17).

Ein Vergleich der pathologischen Veränderungen im Pylorus- und im Fundusteil lässt erkennen, dass im Vorkommen der Entzündungszellen in den beiden Magenabschnitten kein deutlicher Unterschied nachzuweisen ist. Die atrophischen Veränderungen sind dagegen im Fundus fast immer hochgradiger als im Pylorus. Nur in 2 Fällen (16, 17) ist die Atrophie in der ganzen untersuchten Schleimhaut vom gleichen Grade.

Duodenum.

Die Brunnerschen Drüsen im Duodenum sind in 14 Fällen Gegenstand der Betrachtung gewesen. In 4 Fällen war der unterste Teil des Duodenums zurückbehalten worden, und daher fehlten in den Präparaten Brunnersche Drüsen. In 8 Fällen konnte in den Drüsen nichts Pathologisches festgestellt werden (1, , 9, 10, 11, 15, 17, 18). In 2 Fällen (2, 4) war das Bindegewebe etwas vermehrt, und in 5 Fällen (3, 4, 5, 6, 16) waren zwischen den Drüsen spärlich Lymphozyten und Plasmazellen zu konstatieren.

Besprechung.

Aus der mikroskopischen Untersuchung ergibt sich, dass pathologische Veränderungen in der Magenschleimhaut bei perniziöser Anämie ein gewöhnlicher Befund sind, obwohl der Grad der krankhaften Prozesse von Fall zu Fall variiert. Das reichliche Vorkommen von Entzündungszellen im interstitiellen Gewebe der ganzen Magenschleimhaut deutet auf eine Gastritis. Aus der Art der Entzündungszellen ist zu entnehmen, dass die Entzündung chronischer Natur ist. Die ausgiebige Sekretbildung im Ober-

flächenepithel des Pylorusteils und das Vorkommen von Darmepithel sowohl im Pylorus- als im Fundusteil weisen ebenfalls auf eine Gastritis hin (Lange, Saltzman). Auch die zahlreichen Russell'schen Körperchen stellen einen Fingerzeig in dieser Richtung dar.

Für das histopathologische Bild ist ein Umbau der Drüsen kennzeichnend. Die Umwandlung ist am leichtesten in den Fundusdrüsen zu beobachten. Die Deckzellen verschwinden, und die Drüsen nehmen ein Aussehen an, das an dasjenige der Fundusdrüsen erinnert. Lange hat Fundusdrüsen dieser Beschaffenheit

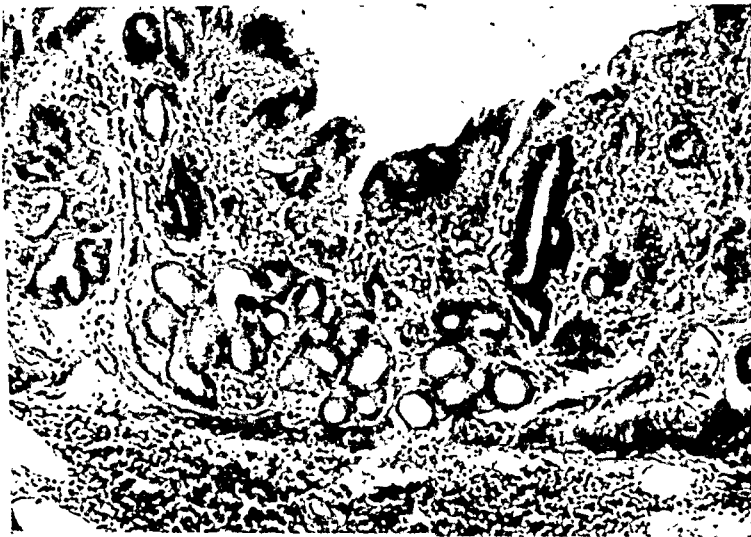


Abb. 9. Fundusschleimhaut aus Fall 9. Die Drüsen hochgradig verändert und in Gruppen gesammelt. Zahlreiche Entzündungszellen in dem interstiellen Gewebe.

ausser bei perniziöser Anämie auch in zwei Fällen von Nephritis festgestellt, aber sie nicht in anderen Fällen von Gastritis gesehen. Die Drüsen werden klein und verkümmern, nehmen einen geschlängelten Verlauf an und sind bisweilen erweitert. Zugleich verraten sie eine Neigung, an Zahl abzunehmen.

Neben den atrophischen Prozessen erscheint oft eine Proliferation der Drüsen, wobei an Trauben erinnernde Drüsenkonglomerate entstehen. Eine solche Drüsengruppe hat eine gewisse Ähnlichkeit mit den Brunnerschen Drüsen im Duodenum. Das Phänomen ist hauptsächlich im Pylorusteil zu beobachten, zeigt sich aber auch, wie aus Abb. 9 hervorgeht, im Fundusteil. Es ist darüber diskutiert worden, ob die Drüsenveränderungen eine Folge

der interstitiellen Veränderungen sind oder ob sie unabhängig von diesen auftreten (Koch, Herzberg, Magnus & Ungley). Lange hat einen ähnlichen Umbau der Drüsen auch bei anderen Formen der Gastritis gesehen, und Hamperl spricht von einer »Umbaugastritis«, wenn die sezernierenden Drüsen in der Magenschleimhaut eine Umgestaltung der eben beschriebenen Art erfahren:

Eine direkte Einwirkung der interstitiellen Veränderungen auf die Drüsenelemente habe ich in Übereinstimmung mit Lange in meinen Fällen nicht feststellen können. Das Bindegewebe ist locker, Zeichen einer Straffung der Drüsenhäuse oder Verschiebungen oder Umgruppierungen der Drüsen durch Narbenschumpfungen sind in dem untersuchten Material nicht zu bemerken. Es scheint mir, dass die Veränderungen, die in den untersuchten Schleimhäuten in den Drüsen zu Gesicht kommen, zu den alternativen und proliferativen Prozessen gerechnet werden müssen, die nebst der Exsudation zur Entzündung gehören.

Nach den hier wiedergegebenen Untersuchungen sind die Veränderungen in der Magenschleimhaut auch in den Pylorusteil lokalisiert. Die exsudativen Prozesse sind in der Pars pylorica ebenso hochgradig wie im Fundus. Die atrophischen Veränderungen sind meistens im Fundusteil ausgeprägter, kommen aber auch im Pylorusteil vor und sind in der Mehrzahl der Fälle wiederzufinden, wenn auch der Grad der Atrophie schwankt. Die proliferativen Prozesse mit einhergehendem Umbau der Drüsen überwiegen im Pylorusabschnitt, wo sie eine gewöhnliche Erscheinung sind.

Meine Resultate weichen also teilweise von den Ergebnissen ab, zu denen Meulengracht auf Grund seiner 8 Fälle von perniziöser Anämie gekommen ist. Wie schon erwähnt, bezeichnet Meulengracht das Pylorusorgan als »recht intakt«. In seinem Material liegen die Drüsen im Pylorusteil wegen der »leicht vermehrten Menge interstitiellen Gewebes« etwas weiter voneinander entfernt als normalerweise. Von dem Vorkommen der Exsudatzellen in der Schleimhaut erwähnt Meulengracht, es bestehe »kein Zweifel, dass die interstitiellen gastritischen Veränderungen sich in allen Fällen in den Pylorusteil hinab fortsetzen«. Die Pylorusdrüsen haben »ihre normale Form und ihr normales Aussehen bewahrt. Man sieht keine Deformation und keinen Umbau, keine zystischen Erweiterungen, und kommt man in die Nähe der Muscularis mucosae

hinunter, wo sich die Drüsen alveolär teilen, so sieht man dem Aussehen nach ähnliche Drüsenlumina in gewöhnlichen kleinen Gruppen liegen wie die kleinen Lobuli. Es ist möglich, dass sie in manchen Fällen mit einer gewissen Reduktion an Zahl und Ausdehnung auftreten, aber eine grössere Reduktion habe ich (Meulengracht) jedenfalls nicht nachweisen zu können geglaubt.» Meulengracht findet also in seinen Fällen Zeichen einer Entzündung in Form von Infiltraten mit Entzündungszellen und ausserdem vielleicht eine leichte Atrophie der Pylorusdrüsen mit einer entsprechenden Vermehrung des interstitiellen Gewebes. Dagegen hat er keine Drüsengänge von verändertem Aussehen bemerkt oder sie umgruppiert gefunden. Ebenso wenig ist ihm eine Drüsenproliferation oder eine ausgeprägtere Atrophie aufgefallen. In dieser Beziehung unterscheiden sich unsere Untersuchungsergebnisse voneinander.

Es wäre von Interesse, die Ursache hierfür zu ermitteln zu suchen. In meinem Material sind Drüsen von verändertem Aussehen nicht in allen Fällen anzutreffen. Vielleicht ist Meulengracht in seinem vergleichsweise kleinen Material auf die leichten Fälle gestossen? Man kann auch annehmen, dass wir unsere mikroskopischen Befunde verschieden gedeutet haben. Solche Drüsengruppen, wie sie z. B. in Abb. 3—7 zu sehen sind, fasse ich als pathologisch auf. Sie weichen meines Erachtens offensichtlich von normalen Pylorusdrüsen ab. Meulengracht beschreibt kleine Drüsengruppen, die kleine Lobuli über der Muscularis mucosae bilden. Vielleicht meint er damit gerade diese meiner Ansicht nach pathologischen Bildungen? Leider hat Meulengracht unter den schönen Photogrammen seiner Veröffentlichung keine Übersichtsbilder von Pylorusschleimhaut.

Möglicherweise bestehen auch Verschiedenheiten in unserem Material. Von meinen Fällen sind 17 nicht mit Leber- oder Magenpräparaten behandelt worden, während in Meulengrachts Material, das aus den Jahren nach der Einführung der Lebertherapie stammt, wahrscheinlich alle Fälle zu therapeutischem Zweck antianämische Organpräparate erhalten haben. In einem vor kurzem veröffentlichten Fall konnte ich sehen, wie sich die für perniziöse Anämie charakteristische glatte Zunge während der Leberbehandlung zurückbildete. In das Kriegslazarett, an dem ich tätig war, kam im Winter 1942 ein junger Soldat mit einer hochgradigen, durch

Bothriocephalus verursachten Anämie. Der Hämoglobinwert betrug bei der Aufnahme 16. Die Zunge war glatt. Es konnten niedrige, abgerundete Papillen festgestellt werden, aber die verhornten Epithelfortsätze fehlten vollständig. Nach Wurmkur und Injektionen von Leberpräparat erholte sich der Patient schnell. Einige Wochen nach der Aufnahme war er wiederhergestellt und hatte die Zunge wieder ihr normales Aussehen mit wohlentwickelten Papillen mit deutlichen grauen Epithelfortsätzen an den Spitzen der Papillae filiformes angenommen. Aus meiner früheren Untersuchung geht hervor, dass die bei perniziöser Anämie in der Schleimhaut der Zunge vorkommenden Veränderungen als Entzündung mit Atrophie des Epithels gedeutet werden können. Vielleicht können auf ähnliche Weise im Pylorusteil der Magenschleimhaut in Fällen, in denen sich die pathologischen Prozesse nicht zu weit entwickelt haben, die Drüsen ihr normales Aussehen wieder annehmen, wenn dem kranken Organismus antiperniziös-anämischer Faktor zugeführt wird. Möglicherweise ist es mehr als ein Zufall, dass in meinem Material in Fall 18 keine Drüsenatrophie im Pylorusteil nachgewiesen werden konnte, dem einzigen meiner Fälle, der viele Jahre mit Magen- oder Leberpräparaten behandelt worden war.

Magnus und Ungley hatten in 7 Fällen von perniziöser Anämie weder Zeichen von Gastritis noch Drüsenatrophie in der Pyloruschleimhaut gefunden. Da die genannten Forscher keine Kasuistik und keine Beschreibung ihrer Präparate mitteilen, kann das Untersuchungsergebnis hier nicht näher geprüft werden. Es scheint jedoch eigentümlich, dass auch der Fundusteil völlig frei von zellulärer Infiltration gewesen sein sollte. Über gastritische Veränderungen im Fundusteil bei perniziöser Anämie sind nämlich alle anderen Forscher einig.

Im Duodenum habe ich, mit Meulengracht übereinstimmend, keine oder nur unbedeutende Veränderungen in den Brunnerschen Drüsen gefunden. Das Bindegewebe war in ein paar Fällen zwischen den Acini etwas vermehrt, und in einigen Fällen wurden leichte entzündliche Veränderungen in Form lichtgestellter Infiltrate von Lymphoidzellen zwischen den Drüsengängen konstatiert, während in der Mehrzahl der Fälle keine pathologischen Veränderungen zu entdecken waren. Mein Material eignet sich nicht zur Beurteilung der Menge des Drüsengewebes in dem ganzen

Brunnerschen Drüsenapparat, da es nicht für einen solchen Zweck aufbewahrt worden war. In Fall 17, in dem das ganze Duodenum zurückbehalten wurde, fanden sich zahlreiche Brunnersche Drüsen. In Fall 18, der auf dieselbe Weise aufbewahrt wurde, war die Zahl der Drüsen wesentlich geringer.

Auf Grund der Feststellungen, die bei zahlreichen therapeutischen Versuchen gemacht worden sind, können wir annehmen, dass Castles »intrinsic factor« von dem Pylorusdrüsenorgan gebildet wird. Es ist daher von grossem Interesse, nachzusehen, ob die pathologischen Veränderungen, die in meinem Material in der Pylorusschleimhaut auftreten, von der Art sind, dass sie störend auf die Funktion der Pylorusschleimhaut einwirken können. Eine bestimmte Äusserung in irgendeiner Richtung gestattet mein Material nicht. Eine histologische Untersuchung kann wertvolle Aufschlüsse über die Funktionen einer Drüse liefern, aber das Material muss dann auf ganz andere Weise zurückbehalten werden. Die Zellen sind lebend zu fixieren und Teile des untersuchten Organs »lebenswarm« in geeignete Fixierflüssigkeiten einzusenken. In meinem Material lässt sich zwar noch konstatieren, ob die Zellen Schleim produzieren oder nicht, aber es ist nicht zu entscheiden, ob die Pylorusdrüsen auch eine andere Funktion gehabt haben. Es ist jedoch bekannt, dass die Arbeit einer Drüse durch entzündliche Prozesse im Drüsengewebe gestört wird. Eine Mastitis setzt die Milchproduktion in der Brustdrüse herab, ein Patient, der eine akute Parotitis bekommen hat, klagt über Trockenheit im Munde. Die Gallensekretion ist bei einer Hepatitis gestört. Eine akute Nephritis führt zu Niereninsuffizienz oder vollständiger Anurie. Betrachten wir in den untersuchten Magen die Pylorusschleimhaut als ein sezernierendes Organ, so ist auf Grund der pathologischen Befunde meiner Untersuchung dargelegt worden, dass die Schleimhaut Sitz einer Entzündung ist, die sich nicht nur durch das Auftreten von Exsudatzellen zu erkennen gibt, sondern in der Mehrzahl der Fälle auch Veränderungen in der Zahl und dem Bau der sezernierenden Drüsen bewirkt. Lange konnte nachweisen, dass die Pepsinsekretion früher als die Salzsäuresekretion auf entzündliche Veränderungen in der Schleimhaut reagiert. In 3 Fällen von Gastritis, in denen Hypersekretion mit hohen Salzsäurewerten im Mageninhalt konstatiert werden konnte, fand Lange interstitielle Infiltrate von Entzündungszellen

und etwas reichlicheres interstitielles Gewebe als gewöhnlich. Die Drüsen zeigten nur eine Andeutung von Atrophie und waren dem Aussehen nach nur unbedeutend verändert. In der Pylorus-schleimhaut sind die Drüsenveränderungen in meinem Material ausgeprägter als in den eben erwähnten genau beschriebenen 3 Fällen Langes. Man darf mithin annehmen, dass die pathologischen Veränderungen in der Pylorus-schleimhaut hochgradig genug sind, um eine mangelnde Funktion der Pylorusdrüsen zu erklären.

Meulengracht hat die Bezeichnung »Pylorusdrüsenorgan« als gemeinsamen Namen für die Pylorusdrüsen und die Brunnerschen Drüsen eingeführt, da angenommen wird, dass sie dieselbe Funktion haben. Nun zeigt sich jedoch in meinem Material, dass die Pylorusdrüsen in manchen der Fälle eine deutliche Atrophie und ein verändertes Aussehen aufweisen, während die Brunnerschen Drüsen sich wenigstens histologisch als normal darstellen. Es ist in der Pathologie ein bekannter Sachverhalt, dass verschiedene Teile gleichartigen Drüsengewebes bei Bedarf füreinander vikariieren. Wenn die eine Niere ausser Funktion gesetzt wird, vergrössert sich die andere. Wenn bei einem Versuchstier Leberparenchym operativ entfernt wird, entwickelt sich in dem zurückgelassenen Lebergewebe eine kompensatorische Hyperplasie. Ist die Funktion der Pylorus-schleimhaut herabgesetzt, so müsste in den Brunnerschen Drüsen eine kompensatorische Hyperplasie auftreten. In meinem Material deutet nichts auf ein solches Verhalten.

Unter den Histologen scheint keine volle Einigkeit über die Identität der Pylorus- und der Brunnerschen Drüsen zu herrschen. Plenk führt in Möllendorffs grossem Handbuch eine Reihe Forscher an, nach denen die eben erwähnten Drüsen der gleichen Art sind, nennt aber gleichzeitig auch eine ziemlich grosse Anzahl von Forschern, die Verschiedenheiten in den Zellen beider Drüsen nachgewiesen haben und daher entgegengesetzter Meinung sind. Vielleicht ist somit die Funktion der Pylorusdrüsen und der Brunnerschen Drüsen nicht ganz gleichwertig.

Es gibt mehrere Beispiele dafür, dass die verschiedenen Abschnitte des Digestionsapparats einander beeinflussen können. Petri und Mitarbeiter haben bei Tierexperimenten gezeigt, dass totale und partielle Resektion des Duodenums konstant Achylie zur Folge hat. Die Duodenalwand produziert Sekretin, das auf

die Pankreassekretion einwirkt. Gross konnte bei Versuchen mit Hunden nachweisen, welche Rolle die Pars pylorica für die Sekretion des Fundusteils spielt. Wenn der Fundus und die Pars pylorica auf operativem Wege voneinander getrennt werden, entsteht eine lebhaftere Sekretion im Fundusteil, wenn Fleischextrakt in den Pylorusteil eingeführt wird, während Fleischextrakt bei direkter Einbringung in den Fundusteil keine nennenswerte Sekretion hervorruft. Meulengracht stellt die Hypothese auf, dass die Funktion des Pylorusdrüsenorgans vielleicht durch einen hormonalen »Schrittmacher« der Sekretion geregelt wird, und wirft die Vermutung auf, dass das betreffende Hormon möglicherweise im Fundusteil des Magens gebildet wird. Nun ist die Pylorusschleimhaut, wie aus meinem Material hervorgeht, bei perniziöser Anämie in der Tat pathologisch verändert und ihre Funktion daher wahrscheinlich gestört. Meulengrachts Hypothese über einen »Schrittmacher« muss infolgedessen noch etwas weiter geführt werden. Nehmen wir hypothetisch an, dass der Pylorusteil im Magen die Funktion der Brunnerschen Drüsen beeinflusst und die Pars pylorica pathologisch verändert ist, so würde dann auch die Funktion der Brunnerschen Drüsen gestört und dadurch auch die Produktion von antianämischem Faktor vermindert oder aufgehoben werden können. Das normale Aussehen der Brunnerschen Drüsen und das Nichtvorhandensein einer supponierten kompensatorischen Hyperplasie würde hierdurch seine Erklärung finden.

Zusammenfassung.

Die pathologischen Veränderungen der Magenschleimhaut sind bei der perniziösen Anämie ein gewöhnlicher Befund, obwohl ihr Grad Schwankungen zeigt. Auch im Pylorusteil ist die Schleimhaut Sitz einer Infiltration von Exsudatzellen. Drüsenatrophie und proliferative Prozesse mit Umbau der Drüsen stellen in der Pars pylorica eine häufige Erscheinung dar. Die Veränderungen in der Pylorusschleimhaut legen die Annahme nahe, dass eine gestörte Funktion der Pylorusdrüsen besteht.

Im Duodenum sind die Brunnerschen Drüsen intakt oder in manchen Fällen Sitz nur leichter entzündlicher Veränderungen.

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(From the Biological Institute of the Carlsberg Foundation, Copenhagen)..

On the Action of Thrombin and Thrombokinase in vivo.

By

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While it was early recognised that the clotting-active tissue factor (thrombokinase, thromboplastin) acted both *in vitro* and *in vivo* as a powerful clotting agent [see, f. inst., Dold & Kodama (1913) and Mills (1919, 1921)] the action of thrombin *in vivo* has been a disputed question.

Mills thus denies that thrombin *in vivo* induces coagulation and then advocates the old theory of Wooldridge about the clotting of blood, according to which thrombokinase acts directly upon fibrinogen [cf. Mills and Guest (1921)]. Also Pickering is unable to obtain intravascular coagulation with thrombin [see Pickering (1925, 1928) and Pickering & Hewitt (1921, 1922)].

In reality, however, this question had been solved already by Edelberg in 1880 in investigations under the direction of Alexander Schmidt after the latter's discovery of thrombin [cf. Alexander Schmidt (1892)]. It was here found that while weak thrombin solutions did not give intravascular coagulation, strong solutions reacted promptly. Apparently these investigations were not known by the authors mentioned, and it therefore remained for J. Mellanby (1933) to settle this question by using potent thrombin solutions prepared after his own method.

Of the thrombin preparation used by Mellanby 0.01 mg clots one ml. of oxalated ox plasma in 30 seconds and corresponds therefore to about the same amount of thrombin as our original thrombin unit [Astrup & Darling (1940, 1941)]. On intravenous injection in rabbits weighing about 2 kg of 1.5 to 3 mg of such a preparation, corresponding to about 150 to 300 thrombin units, the animals die of intravascular coagulation in 2 to 7 minutes. Small amounts, however, give no coagulation but increase the clotting tendency of the blood, and are followed after 20 minutes by a negative phase in which the blood does not clot at all, presumably because of exhaustion of the fibrinogen content of the blood plasma. In a few hours the coagulability is again restored. It is not possible by repeated injections of thrombin to develop immunity against the action of thrombin.

Some years later *Crut* (1939 a, b) reported experiments which are not concordant with the findings of Mellanby. His most potent solutions clot the double amount of oxalated plasma in 2–3 seconds, which corresponds to more than 20 to 30 thrombin units per ml. On intravenous injection in dogs he finds first an increased clotting time for the blood, and after 15 to 20 minutes a diminution of fairly long duration. Also the bleeding time is decreased. He does not find any sign of intravascular coagulation but assumes that the viscosity of the blood is increased. It seems highly improbable that thrombin should have such an effect, as the fibrin formed immediately will adhere to the walls of the vessels and to the cellular elements when not deposited as a real thrombus. Further, one of his experiments — Exp. 3, Table 1 — indicates most likely an intravascular coagulation. The amounts injected range from 1 to 4 ml. per kg., *i. e.*, about 20–120 thrombin units per kg, which is a rather small dose. He tries to use thrombin as a hemostatic agent, a possibility which had already been mentioned by *Pickering* (1928).

Lenggenhager (1935) obtains intravascular clotting by injection of thrombokinase or thrombin in rabbits, and assumes the toxic properties of tissue extracts or fresh serum to be due to the presence of these substances. Clots are found especially in the right half of the heart and in the pulmonary arteries. The animal survives injection of small amounts, but then necrotic areas in the

lungs are found. His results are only partially confirmed by Dyerhoff and co-workers (1939).

At the same time thrombin was investigated and recommended as a hemostatic agent by Seegers, Warner, Brinkhous & Smith (1939) and Warner, Brinkhous, Seegers & Smith (1939). They measured the potency in their own units (*Iowa Units*) which are probably smaller than our units. Rapid injection of 250 units into the jugular vein of a rat resulted in death in one minute. Clots were found in the right ventricle and in the pulmonary artery. Injection of 100 units produced no obvious disturbance.

Experimental.

In our experiments a thrombin preparation B, made as described before, was used [Astrup & Darling (1940, 1941, 1942)]. It contained about 10 thrombin units per mg of substance, and most of it was obtained from »Løvens kemiske Fabrik», Copenhagen. The thrombokinase (thromboplastin) employed was prepared from rabbit lung in the same manner as described for ox lung [Astrup & Darling (1942 a)]. Examples of the action of thrombin and thrombokinase follow. Rabbits weighing about 2.5 kg. were used. Ethyl ether was used for anesthesia.

Thrombin.

1. In a rabbit 2 ml. of a thrombin solution containing 120 T.U. per ml. (= 240 T. U.) are injected rapidly in the left *vena femoralis*. The animal dies in the course of 1—2 minutes under spasms and convulsions. Only minor clots and fibrin threads in the right ventricle and the lung vessels are found.

2. In the left jugular vein 120 T. U. dissolved in 3 ml. (*i. e.* 40 T. U. per ml.) of 0.9 per cent NaCl are injected very slowly in the course of about 10 minutes. During the injection a thrombus is formed in the vein which feels solid and distended. The wound is then closed, and the animal seems to be feeling well after the treatment. In about half an hour, however, it suddenly begins to breathe superficially and small convulsions appear, whereupon it dies rapidly. A large embolus is then found in the pulmonary artery, while the vein used for the injection is now empty. The thrombus has thus been loosened and by the blood stream carried to the lung arteries.

3. In two animals 1000 T. U. dissolved in 10 ml. of physiological saline are injected subcutaneously in the thigh. The animals did not respond to this treatment in any way and were in perfect health during the whole observation period (14 days). Two animals showed the same behaviour after intramuscular administration of the same amount. This was also the case after intraperitoneal injection on two animals of the same dose.

4. Slow intracardial injection was then tried. The solution contained 100 T. U. per ml. and 5 ml. were given in the course of 15—20 minutes by means of a Record syringe in which the piston could be moved by a screw. One animal died in convulsion after receiving 0.5 ml. (=50 T. U.). Tiny clots were found in the heart and in the pulmonary arteries, otherwise it was normal. Two died after receiving 2 ml. (= 200 T. U.), but blood was found in the pericardium. Two animals survived the injection (= 500 T. U.) and were in good condition throughout the observation period.

5. Repeated injections of small amounts were given to two animals into an ear vein. The thrombin solution contained 20 T. U. per ml. One animal was given 1 ml. every hour in two series of 6 hours each with an interval of 18 hours, thus receiving a total of 12 injections. In another animal an injection was made in the same manner every half hour, thus making a total of 24 injections. None of these animals showed any sign of circulatory disturbances, and afterwards they were also in good condition.

Thrombokinase.

6. In an ear vein of a rabbit 0.1 ml of a rabbit thrombokinase is injected (prepared as described before). The animal dies with convulsions in a few minutes after the injection.

7. The thrombokinase is now diluted three times, and with an interval of two minutes the following amounts are injected in an ear vein: 0.1, 0.2, 0.2, 0.3, 0.3 and 0.4 ml. After the last injection the animal dies showing the usual symptoms. The same does an animal receiving the following doses: 0.1, 0.1, 0.2, 0.2, 0.3, 0.3, 0.4, 0.5, 0.6, 0.8, 1.2 and 1.5 ml., and another receiving: 0.1, 0.1, 0.2, 0.2, 0.3, 0.3, 0.4 and 0.5 ml. All the animals show solid thrombi in the veins of the neck.

8. Undiluted thrombokinase was given intracardially in four rabbits with a screw syringe. One ml. was given in the course of 15—20 minutes. Two animals died in convulsions after receiving 0.3 ml. and large solid thrombi were found in the heart and pulmonary vessels. The two other animals showed slight convulsions during the injection and seemed a little weak afterwards, but they recovered and were then perfectly healthy during the whole observation period (14 days).

9. A thrombokinase diluted 10 times was tried by injection in an ear vein. One animal received 0.5 ml and died then in the course of 5 minutes.

Another animal was given 0.5 ml every hour in 2×6 hours with an interval of 18 hours. Total 12 injections. The animal showed no sign of circulatory disturbances, neither during the injection nor during the observation time. The same was the case with a third animal receiving 0.5 ml in the same manner every half hour, a total of 24 injections.

Discussion.

From the experiments reported, it is quite evident that both thrombin and thrombokinase are very toxic substances when injected intravenously, and that it is just as easy to obtain intravascular coagulation by using potent thrombin solutions as by using thrombokinase. However, it is also seen that the injections show a great variation in effect from one individual to another, possibly due to the mode of injection and the condition of the animal in question. Thus, it is seen that intravenous injection of either thrombin or thrombokinase is fatal in almost every case, and only by using small amounts of very dilute solutions is it possible in some cases to avoid subsequent death of the animal. But even here the tolerance of the animals varies greatly from experiment to experiment. Thrombin administered in this manner (Exp. 5) is possibly better tolerated than thrombokinase (Exp. 9). This is no wonder, as blood plasma contains a powerful antithrombin, so that one single ml. of plasma is able to inactivate about 150 T. U. in the course of 15 minutes at 37° [Astrup & Darling (1942 c), Volkert (1942)]. Intravascular coagulation can therefore be obtained by amounts of thrombin which are very much smaller than the total amount that may be inactivated by the antithrombin present in the blood. This is because the inactivation is a relatively slow process, while thrombin reacts immediately with fibrinogen. As there is no anti-thrombokinase in blood, thrombokinase acts in another manner and may, even in small doses, in a relatively short time give rise to considerable amounts of thrombin.

Large amounts of thrombin may be given subcutaneously, intramuscularly or intraperitoneally without intravascular coagulation resulting (Exp. 3), but intracardial injection is the only relatively safe way of administering larger amounts of thrombin or thrombokinase in the blood stream (Exp. 4 and 8). This mode of

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6. In an ear vein of a rabbit 0.1 ml of a rabbit thrombokinase is injected (prepared as described before). The animal dies with convulsions in a few minutes after the injection.

7. The thrombokinase is now diluted three times, and with an interval of two minutes the following amounts are injected in an ear vein: 0.1, 0.2, 0.2, 0.3, 0.3 and 0.4 ml. After the last injection the animal dies showing the usual symptoms. The same does an animal receiving the following doses: 0.1, 0.1, 0.2, 0.2, 0.3, 0.3, 0.4, 0.5, 0.6, 0.8, 1.2 and 1.5 ml., and another receiving: 0.1, 0.1, 0.2, 0.2, 0.3, 0.3, 0.4 and 0.5 ml. All the animals show solid thrombi in the veins of the neck.

8. Undiluted thrombokinase was given intracardially in four rabbits with a screw syringe. One ml. was given in the course of 15—20 minutes. Two animals died in convulsions after receiving 0.3 ml. and large solid thrombi were found in the heart and pulmonary vessels. The two other animals showed slight convulsions during the injection and seemed a little weak afterwards, but they recovered and were then perfectly healthy during the whole observation period (14 days).

9. A thrombokinase diluted 10 times was tried by injection in an ear vein. One animal received 0.5 ml and died then in the course of 5 minutes.

Another animal was given 0.5 ml every hour in 2×6 hours with an interval of 18 hours. Total 12 injections. The animal showed no sign of circulatory disturbances, neither during the injection nor during the observation time. The same was the case with a third animal receiving 0.5 ml in the same manner every half hour, a total of 24 injections.

Discussion.

From the experiments reported, it is quite evident that both thrombin and thrombokinase are very toxic substances when injected intravenously, and that it is just as easy to obtain intravascular coagulation by using potent thrombin solutions as by using thrombokinase. However, it is also seen that the injections show a great variation in effect from one individual to another, possibly due to the mode of injection and the condition of the animal in question. Thus, it is seen that intravenous injection of either thrombin or thrombokinase is fatal in almost every case, and only by using small amounts of very dilute solutions is it possible in some cases to avoid subsequent death of the animal. But even here the tolerance of the animals varies greatly from experiment to experiment. Thrombin administered in this manner (Exp. 5) is possibly better tolerated than thrombokinase (Exp. 9). This is no wonder, as blood plasma contains a powerful antithrombin, so that one single ml. of plasma is able to inactivate about 150 T. U. in the course of 15 minutes at 37° [Astrup & Darling (1942 c), Volkert (1942)]. Intravascular coagulation can therefore be obtained by amounts of thrombin which are very much smaller than the total amount that may be inactivated by the antithrombin present in the blood. This is because the inactivation is a relatively slow process, while thrombin reacts immediately with fibrinogen. As there is no anti-thrombokinase in blood, thrombokinase acts in another manner and may, even in small doses, in a relatively short time give rise to considerable amounts of thrombin.

Large amounts of thrombin may be given subcutaneously, intramuscularly or intraperitoneally without intravascular coagulation resulting (Exp. 3), but intracardial injection is the only relatively safe way of administering larger amounts of thrombin or thrombokinase in the blood stream (Exp. 4 and 8). This mode of

administration has also been tried by Mills (1919). In this manner the active substance, injected slowly, is immediately diluted by the rapidly flowing blood. The concentration in the blood of thrombin injected or formed by the thrombokinase is therefore small, and in no place a high local concentration appears. The antithrombin present is able to inactivate a great deal of the thrombin and the fibrin formed from the small concentration of thrombin is deposited on the walls of the vessels and on the blood cells and does not form real, solid clots and thrombi. In two further cases an animal died with convulsions in connection with an intracardial injection of thrombin. This was found to be due to an anaphylactic shock, as the animals had been treated previously with injections of ox plasma and casein respectively. The species specificity of the proteins are therefore retained even through the procedures used for the preparation and purification of the thrombin, and an anaphylactic shock may be elicited by such a remotely related protein as ox casein.

Like most investigators, we have as a rule found the clots in the right ventricle and in the pulmonary arteries. We are of the opinion that the thrombi are formed at the site of the injection or in its immediate neighbourhood, and that they are then carried centrally by the blood stream and deposited in the heart and in the pulmonary arteries. Such an event is shown to happen in Exp. 2.

For the rabbit thrombokinase used no units are given. But it is made in the same manner as an ox thrombokinase containing about 350 kinase units per ml. according to Astrup & Darling (1942 a). As the action of thrombokinase on prothrombin is to a great extent uninfluenced by species specificity it is not possible to measure the action of rabbit thrombokinase on rabbit blood by comparison with its action on ox plasma, and no investigations concerning the possibility of expressing its strength in units based on rabbit plasma have been made. We have also tried injection into the ear vein of a thrombokinase prepared from ox brain (Astrup, to be published later) but without intravascular coagulation (which may be due to a too weak preparation and its origin from a foreign species).

In none of our cases have we investigated the prothrombin and fibrinogen content of the blood during the treatment, but the anti-

thrombin content has been measured and shown to be of interest in the study of thrombosis [Volkert (1943)].

A few investigations concerning the use of thrombin as a hemostatic agent have been published by Crut and the Iowa-authors (l. c.). An extensive investigation on the possibility of using our thrombin in this manner has now been made recently by Selso (1943) with promising results. As a supplement to his investigations our results are published in order to obtain a more thorough knowledge of the action of these substances *in vivo*, and to point out the very dangerous properties of potent preparations, which means that they must be handled with caution.

Summary.

Potent thrombin solutions give intravascular clotting just as easily as do thrombokinase solutions. This property is investigated and discussed in the light of earlier and recent experiments. Only by intracardial injection it is possible to administer potent solutions of these substances in the blood stream with any degree of safety.

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Aus der Medizinischen Abteilung des Inselspitals Bern:
Prof. A. Schüpbach.

Hyperkalzaemie und Organverkalkungen bei Boeckscher Krankheit.

Von

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(Bei der Redaktion am 27. Mai 1943 eingegangen).

Wir berichten im folgenden über eine eigenartige Störung des Mineralstoffwechsels bei Boeckscher Krankheit, die wir in einem relativ kleinen Material dreimal beobachten konnten. Analoge Feststellungen sind bisher nur von Harrell und Fisher und von v. Creveld mitgeteilt worden. Über die ophthalmologischen Verhältnisse bei Fall 1 und 3 der hier wiedergegebenen Kasuistik hat Dr. Haldimann aus der Berner Augenklinik (Prof. Goldmann) an anderer Stelle berichtet.

Bestimmt handelt es sich bei dieser Störung des Mineralstoffwechsels im Verlaufe des Morbus Boeck um keinen regelmässigen, sondern um einen seltenen Befund. Nach der Demonstration zweier unserer Fälle an der Tagung der Schweizerischen Gesellschaft für innere Medizin durch Schüpbach ist an verschiedenen Kliniken eine Nachprüfung erfolgt, die bisher keine positiven Resultate mehr ergeben hat. Trotzdem möchten wir nach den gleichsinnigen Publikationen von Harrell und Fisher sowie v. Creveld ein zufälliges Zusammentreffen ablehnen.¹

¹ Es besteht die Aussicht, weitere Fälle von Hyperkalzaemie bei Morbus Boeck zu erfassen, wenn bei allen Boeck-Kranken der sehr einfach auszuführende Sulkovitch-Test (cit: bei Albright) auf Hyperkalziurie periodisch durchgeführt und bei positivem Ausfall die Bestimmung des Blutkalziumspiegels

Es liegt nicht in unserer Absicht, im Rahmen dieser Mitteilung die Ätiologie der Boeckschen Krankheit im allgemeinen zu erörtern. Nach der in den letzten Jahren, besonders auch im deutschen Schrifttum am häufigsten vertretenen Auffassung handelt es sich dabei um eine eigenartige Form der Tuberkulose mit gutartigem Verlauf und meist negativer Tuberkulinreaktion. Wir möchten aber an dieser Stelle auch auf die nicht unbeträchtlichen Schwierigkeiten aufmerksam machen, die dieser Auffassung entgegenstehen. Bezüglich aller Einzelheiten sei auf die zusammenfassende Darstellung Pautriers, eines ausgezeichneten Kenners dieses Gebietes, verwiesen.

1) *Hans H., geb. 1904*, ein leicht debiler Bauernknecht, war bis zum Beginn seines jetzigen Leidens stets gesund. Dieses setzte im Jahr 1934 schleichend mit Müdigkeit und Durst, Husten, Stechen auf der Brust, leichter Dyspnoe und subfebriler Temperatur ein. Unsere erste Untersuchung ergab drei Monate später bei dem mittelgrossen asthenischen Mann *multiple Drüsenschwellungen, eine leicht vergrösserte derbe Leber und einen grossen, bis zum Darmbeinkamm reichenden, derben und höckrigen Milztumor*. Daneben zeigte die Röntgenaufnahme des Thorax eine frische miliare Aussaat in allen Lungenfeldern und einen verkalkten Primärkomplex links. Trotz dieses scheinbar sehr ernsten Befundes fühlte sich der Patient nie ernstlich krank, und es erfolgte eine so weitgehende Besserung des Allgemeinzustandes, dass er nach 10 Wochen unter der *Diagnose einer benignen Miliartuberkulose (Granulie froide)* nach Hause entlassen werden konnte. Dort arbeitet er seither, von kurzen Unterbrüchen abgesehen, bei kaum gestörter Gesundheit auf dem kleinen Landwesen seiner Eltern. Durch vielfache periodische Nachuntersuchungen bot sich uns Gelegenheit, den Krankheitsverlauf bis zum heutigen Tage, also während 9 Jahren, zu beobachten.

Zahlreiche *Sputumuntersuchungen auf Tb-Bazillen* ergaben im direkten Ausstrich, in der Kultur sowie im Tierversuch stets *negativen Befund*. Auch

angeschlossen würde. Das Sulkovitch-Reagens (Oxalsäure 2.5, Ammoniumoxalat 2.5, Acid. acet. glac. 5 cm³, Aq. dest. ad 150 cm³) wird zu gleichen Teilen dem Urin beigelegt. Bei normaler Kalziurie entsteht nach einigen Minuten eine leichte Opaleszenz, bei Hyperkalziurie eine milchige Trübung, bei abnorm niedriger Kalkausscheidung bleibt das Gemisch vollständig klar. Nach Sulkovitch, der diese Probe für seine unter AT 10-Behandlung stehenden Tetaniekranken zur ständigen Selbstkontrolle ausgearbeitet hat, kann aus dem Verhalten der Kalziurie praktisch weitgehend auf den Blutkalkspiegel geschlossen werden. Opaleszenz würde demnach normalen Blutkalkwert, milchige Trübung Hyperkalzaemie und fehlender Niederschlag Hypokalzaemie bedeuten. Vorauszusetzen ist hierbei allerdings eine in Bezug auf den Kalkgehalt normale Ernährung, da abnorm hohe Kalkzufuhr (medikamentös oder z. B. auch bei Genuss grösserer Milchquantitäten) an sich Hyperkalziurie erzeugen kann, und da umgekehrt bei sehr kalkarmer Diät die Kalziurie auf abnorm niedrige Werte absinken kann.

die *Tuberkulinprobe* nach Mantoux blieb dauernd negativ bis zu einer Verdünnung von 1:1000; 1939 wurden noch höhere Konzentrationen intrakutan verabfolgt und reaktionslos ertragen bis zu einer Dosis von 0.1 cm³ ATK 1:10.

Blutbefunde: Normale Leukozytenzahl, zeitweise Neigung zu Leukopenie, dauernd ausgesprochene Monozytose von 11.5 bis 23.5 % (Durchschnitt aus 14 Blutstaten 19.7 %) und Eosinophilie von 3—10.5 % (Durchschnitt 5.75 %). Hgb. und Erythrozyten ohne nennenswerte Veränderung. WaR und zugehörige Ergänzungsreaktionen negativ.

September 1934 *Exzision einer axillären Lymphdrüse.* Histologischer Bericht (Prof. Wegelin): Lymphatisches Gewebe nur noch spärlich vorhanden, grösstenteils ersetzt durch viele dicht stehende kleine Epitheloidzellknötchen mit zahlreichen Langhansschen Riesenzellen. Stroma vermehrt, hyalin, hier und da mit Verkalkungen. Im Bindegewebe und in der Intima der Venen des Hilus ebenfalls Tuberkel. Diagnose: Tuberkulose einer axillären Lymphdrüse (körniges Lymphom).

Von Beginn an bestand ferner eine eigentümliche *Augenerkrankung* (vgl. Haldimann): Knötchen in Konjunktiva, Iris und Chorioidea, ungewöhnliche, mit dichter Trübung einhergehende »Keratitis« (Verkalkung). Abrasio der Kornea: Verkalkung der Bowmanschen Membran. Probeexzision aus der Konjunktiva: das Gewebestück ist von geschichtetem, unverhorntem Plattenepithel bedeckt; darunter lockeres, zellarmes Bindegewebe, infiltriert mit einigen Lymphozyten; ferner Blut und hyalines Fibrin. Im Epithel und im Bindegewebe einzelne Verkalkungen. An einer Stelle unter dem Epithel einige z. T. verkäste Epitheloidzellknötchen mit Langhansschen Riesenzellen. Diagnose: Tuberkulose der Konjunktiva (Prof. Wegelin). Später ebenfalls durch die Augenklinik ausgeführte Probeexzisionen der Konjunktiva ergaben im wesentlichen das gleiche Bild. Ein Unterschied war aber insofern festzustellen, als nunmehr in den Epitheloidzellknötchen jede Spur von Verkäsung fehlte und anderseits die Verkalkungen noch ausgedehnter waren als 1934.

Im Jahre 1937 wurde die *Diagnose*, die bisher auf atypische, auffallend gutartig verlaufende Tuberkulose mit miliarem Schub gelaute hatte, einer Revision unterzogen. Die dauernde Negativität der Tuberkulinprobe, das weitgehende Fehlen von Verkäsung im histologischen Bild des Lymphdrüsen- und Bindehautgewebes, die Gutartigkeit des gesamten Prozesses, der Blutbefund (Monozytose), vor allem aber die so typische Kombination krankhafter Erscheinungen an Lungen, Lymphdrüsen, Milz, Leber und verschiedenen Geweben des Auges veranlasste uns, mit Bestimmtheit einen *Morbus Boeck* von rein viszeralem Typus anzunehmen.

Unser besonderes Interesse hatte ferner eine ebenfalls seit 1934 bestehende *Nierenstörung* erweckt, die nach Art und Verlauf durch die nachfolgende Tabelle gekennzeichnet wird.

Es bestanden demnach seit Beginn eine ausgesprochene Hypostenurie, eine leichte Polyurie, daneben eine anfangs beträchtliche, später etwas zurücktretende Retention harnpflichtiger Substanzen im Blut. Der Blut-

Tab. 1.

	1934	1935	1936	1937	1938	1939	1940	1941	1942
<i>Urinbefunde.</i>									
Tagesmenge cm ³ maxim.	3000	3000	3000		2200	2000	1800	2900	2200
„ „ minim.	1500	1500	1600	1800	1500	1000	1000	1500	1000
spez. Gew. d. Tagesmenge	7—12	5—11	8—10	12	6—10	8—13	10—11	7—10	6—11
sp. G. im Verd. u. Konz. Vers.	9—15	2—11 5—13 5—12	9—14 9—14	11—14	9—11 9—13	13 max.	12 max.	7—11	11 max.
sp. G. d. Einzelportionen während einer Woche		nach 0.5 Pituitrin s.c. 1006, max.			7—11				
<i>Blutbefunde.</i>									
Harnstoff mg %	158 120 120	125 134 115 120	132	120	124 115	142	120	115 82	93 115 129
Harnsäure mg %	4.2	4.0 4.0 5.0	5.0	4.3	5.0 4.0			5.7 4.3	5.2 4.5
Indikan mg %	0.16 0.13	0.64 0.16 0.32 0.64	0.32	0.32	<0.1 <0.1	<0.1	<0.1	0.16	0.1 0.16 <0.1
Rest-N mg %					80.6	88		47 40 56	
Alkalireserve Vol. %									
Blutdruck mm Hg.	180/120 135/85 —170/105	130/95 —150/110	125/90 —150/110	140/95	140/90 —160/110	130/90 —145/110	130/95 —135/95	125/95 —155/110	115/85 —155/115

druck war mit Ausnahme einer noch zu besprechenden initialen Erhöhung stets normal oder nur sehr wenig erhöht. Andere Zeichen kardiovaskulärer Störung nephritischer Art wurden jedoch immer vermisst: Herz radiologisch normal gross; Fundus oculi, so weit bei der vorhandenen Hornhauttrübung eine Beurteilung möglich war, ohne hypertonische oder nephritische Veränderungen. Oedem bestand während der ganzen Beobachtungszeit nie. Auffällige Trockenheit der Haut bei vollkommen fehlender Schweißsekretion.

Urin: leichte Albuminurie während der ganzen Beobachtungszeit (Spuren bis 0.3 ‰ nach Esbach). Im Sediment anfangs mässig viel (10 bis 20 im Gesichtsfeld), später nur noch vereinzelt Erythrozyten. Seit 1936 in zahlreichen Urinproben sehr viele Oxalatkristalle. Annahme einer anhypertonischen chronischen Nephritis.

1938 afebrile sehr schmerzhafte *trockene Pleuritis* rechts, nachdem auch früher schon mehrfach pleuritische Reiben festgestellt worden war.

Im Jahre 1939 wurde erstmals eine Bestimmung des *Serum-Kalziums* ausgeführt und dabei der stark erhöhte Wert von 16.3 mg % festgestellt; Phosphor 4.3 mg %.

Damit war für die eigentümlichen *Verkalkungsvorgänge* im *Auge* eine gewisse Erklärung gebracht. Leichter verständlich wurde ferner die aussergewöhnliche *Umwandlung des radiologischen Lungenbefundes*, bei dem sich die ursprünglich aus miliaren Fleckschatten zusammengesetzte Aussaat im Verlauf der Jahre zu einem äussert feinkörnig granulierten Bilde entwickelt hatte, das wir als *miliare Kalzinose* ansprechen.

Weitere mit dieser Mineralstoffwechselstörung in Zusammenhang stehende Organveränderungen konnten am *Skelet* festgestellt werden. Dieses zeigte eine in ihrer Art sehr ungewöhnliche, mit Kalkvermehrung einhergehende Störung des Knochenbaues. Schon in frühern Röntgenaufnahmen, die zum Zwecke des eventuellen Nachweises einer Jünglingschen Ostitis angefertigt worden waren, hatte man ähnliche, damals noch weniger stark ausgeprägte Veränderungen bemerkt. In den Aufnahmen vom Jahre 1940 fand sich in allen Skeletteilen, vorzüglich aber in Fuss- und Handwurzelknochen, sehr deutlich jedoch auch im Bereich der Hüftgelenke und der Wirbel eine wolkig angeordnete hochgradige Vermehrung der schattengebenden Substanz. Alle Knochen erschienen auf diese Weise sehr stark verdichtet, die Femurköpfe z. B. nahezu opak. Da es sich bei den beschriebenen Veränderungen vor allem um eine Abweichung der Knochenstruktur handelt, eignen sie sich schlecht zur bildhaften Wiedergabe, die deshalb unterbleibt. Veränderungen im Sinne der Jünglingschen Ostitis cystica wurden während der ganzen Beobachtungszeit vermisst. Drei in der ophthalmologischen Bearbeitung des Falles (C. Haldimann) und anfänglich auch von uns in diesem Sinne gedeutete Aufhellungen eines Metakarpale erwiesen sich später als Projektion einer unregelmässig verkalkten Hautnarbe auf den darunter liegenden Knochen. Eine im Jahr 1942 aus der Tibia im Bereich des Kniegelenkes ausgeführte Probæxzision ergab infolge Kleinheit des Knochenstückes keinen verwertbaren histologischen Befund.

Deutliche durch Kalkablagerungen bedingte Veränderungen kamen ferner in folgenden Organen zum Vorschein: Beide *Nierenschatten*, links z. T. durch den grossen Milztumor überdeckt, erschienen im Röntgenbild auffällig dicht mit vereinzelt aufgesetzten weichen Fleckschatten. Grösse des Organes deutlich vermindert. Im mittleren Epigastrium waren ohne Kontrastfüllung die *Längsfalten des Magens* deutlich als schattengebende Streifen erkennbar, und schliesslich erzeugte auch die stark vergrösserte Milz einen dichteren Schatten, als dies für Milztumoren dieser Grösse sonst zutrifft. Hochgradige Verkalkung wiesen ferner die grossen und kleinen *Arterien* der Extremitäten und des Stammes auf. So waren z. B. im Trapezius auf der Thorax-Röntgenaufnahme zahlreiche geschlängelt verlaufende kalkdichte Gefassschatten von 2–3 mm Durchmesser erkennbar.

Sehr deutlich sichtbare, feinkörnige Verkalkungsprozesse fanden sich ausserdem im *periartikulären Gewebe* der Fusswurzel- und der Sprunggelenke. Schliesslich wurde vom Otologen in beiden *Trommelfellen* eine kreisförmig den Hammergriff umgebende, scharf begrenzte Verkalkungszone festgestellt, die sich ohne weiteres von den gelegentlich vorkommenden bannigen Kalkablagerungen unterscheiden liess.

Die Nachprüfung der Kalzaemie im November 1940, im Juni und September 1941 ergab die folgenden Werte: 12 und 13.6; 14.4; 12.4 mg % (siehe Tabelle 2). Im November 1946 wurde ferner die quantitative Bestimmung der Kalzintie bei einer von Snapper angegebenen kalkarmen Standarddiät ausgeführt, wobei sich an drei aufeinanderfolgenden Tagen die leicht erhöhten Werte von 174, 207 und 233 mg ergeben (Normalwert 100–150 mg, starke Erhöhung vor allem beim Hyperparathyreoidismus bis zu 500 mg im Tag).

Wie im Verhalten der Hyperkalzaemie, so waren auch im Ausmass der Hornhautverkalkung periodische Schwankungen erkennbar. Nach therapeutischer Abtönung blieb oft der Befund während langer Zeit unverändert, um dann später ohne ausseren Anlass sehr rasch wieder an Intensität zuzunehmen. Ein zeitlich gleichsinniges Verhalten von Hyperkalzaemie und Hornhautverkalkung konnte hierbei nicht festgestellt werden.

Erwähnt sei ferner der dauernde Befund einer Atrophie der Zungenpapillen und einer *Achylia gastrica*, sowie der einmalige einer flachen Blutzuckerbelastungskurve (später wieder normal).

Von Interesse durfte schliesslich die Tatsache sein, dass der 12 Jahre ältere Bruder des Patienten im Jahre 1926 ebenfalls eine in Heilung übergehende *Miliartuberkulose der Lungen* durchgemacht hat. Vorübergehend bestand neben der miliaren Aussaat noch ein grösserer Pleuraerguss. *Tb.-Bazillen* konnten auch hier weder im Sputum, noch im Pleuraerguss (Tierversuch) nachgewiesen werden.

Epikrise. Der heute 29-jährige Patient erkrankte 1934 schleichend mit folgenden Erscheinungen: miliarer Lungenaussaat, genereller Lymphdrüsenschwellung, vergrösserter derber Leber, grossem Milztumor, knötchenförmiger Entzündung der Konjunktiva,

Iris und Chorioidea, Verkalkungen in Kornea und Konjunktiva. Während der bis heute 8 Jahre umfassenden Beobachtungszeit verlief das Leiden chronisch und ohne wesentliche Störung des Allgemeinbefindens. Die Diagnose glauben wir mit Bestimmtheit auf Morbus Boeck vom rein viszeralen Typus stellen zu dürfen, und zwar auf Grund der ausserordentlichen Gutartigkeit des Verlaufes, des histologischen Biopsieergebnisses an Lymphdrüsen- und Bindehautgewebe (Epitheloidzellknötchen ohne wesentliche Verkäsung), des dauernden Fehlens von Tb-Bazillen im Sputum, der negativen Tuberkulinproben bis zu einer Konzentration von 0.1 cm³ ATK 1:10 intrakutan, der Blutmonozytose sowie der typischen Kombination krankhafter Erscheinungen an Lungen, Pleura, Lymphdrüsen, Milz, Leber und verschiedenen Geweben des Auges.

Im Jahre 1939 ergab eine erstmalige Bestimmung des Blutkalziumspiegels einen Wert von 16.3 mg %; Phosphor 4.3 mg %. Damit war eine allgemeine Störung des Mineralstoffwechsels aufgedeckt, welche bis zu einem gewissen Grad die Verkalkungsvorgänge an Kornea und Konjunktiva sowie im histologischen Bild der Lymphdrüse, ferner auch die eigentümliche, äusserst feinkörnige Umwandlung des miliaren Lungenbildes (miliare Kalzinose) zu erklären vermochte. Als weitere, in diesen Rahmen gehörende Organverkalkung fand sich an den Nieren und der stark vergrösserten Milz eine höchstwahrscheinlich auf Kalkeinlagerung beruhende, diffus vermehrte Schattengebung im Röntgenbild. Eine analoge Veränderung kann auch für die Magenschleimhaut angenommen werden, die in der Leeraufnahme des Abdomens sehr deutlich in ihrer Längsfaltung erkennbar ist. Ausgedehnte pathologische Kalkablagerungen fanden sich ferner radiologisch in den Arterien fast jeden Kalibers sowie im periartikulären Bindegewebe und direkt sichtbar in beiden Trommelfellen. Sehr ausgesprochene Veränderungen lagen schliesslich im ganzen Skelet vor: wolkig angeordnete, z. T. sehr hochgradige Vermehrung der schattengebenden Substanz.

Seit Beginn der Erkrankung besteht ferner eine sehr chronisch verlaufende ausgesprochene Niereninsuffizienz. Der Blutdruck war anfänglich deutlich, später aber nur noch geringfügig erhöht (Kalk-Schrumpfniere).

2). *Karl H., geb. 1916*, ein früher stets gesunder Mann, erkrankte erstmals im Jahre 1936 mit leichtem Fieber und Husten. Da die Thoraxdurchleuchtung eine beträchtliche *Schwellung der Hilusdrüsen* ergab, erfolgte zunächst — in der Annahme, dass es sich um eine aktive Hilusdrüsentuberkulose handle — die Verlegung in ein Lungensanatorium. Bei kaum gestörtem Allgemeinbefinden blieb dort der Befund vorerst konstant. Ein Jahr später Einweisung auf unsere Spitalabteilung zum Zwecke der Begutachtung. Die jetzt erhobenen Befunde veranlassten uns, von der bisherigen Auffassung des Krankheitsbildes abzurücken und eine Boecksche Krankheit anzunehmen: einmal waren mit der Annahme einer aktiven Tuberkulose der äusserst gutartige Verlauf sowie das fast vollständige Fehlen von Fieber nur schwer vereinbar; anderseits sprach gegen eine solche Annahme auch der zuerst *negative*, später nur bei 1:1000 positive Ausfall der *intra-kutanen Tuberkulinprobe*. Entscheidend war aber neben dem Blutbefund (6500 Leukozyten mit 12,5 % Monozyten) vor allem das Ergebnis der *Probeexzision einer kubitalen Lymphdrüse*: das Drüsengewebe war fast vollständig ersetzt durch zahlreiche, ziemlich scharf abgegrenzte, selten wenig verkäste Epitheloidzelltuberkel mit Lymphozyten und Langhansschen Riesenzellen. Diagnose: Lymphdrüsentuberkulose (körniges Lymphom), Prof. Wegelin.

Die Diagnose eines Morbus Boeck wurde durch den weiteren Verlauf der Affektion in vollem Umfange bestätigt. *Exzision einer okzipitalen Lymphdrüse* im folgenden Jahr: Epitheloidzelltuberkel mit Langhansschen Riesenzellen, im Zentrum der Knötchen konjunktivales Hyalin. Untersuchung auf Tb-Bazillen (inkl. Tierversuch) vollkommen negativ. 1939 Feststellung eines den Rippenbogen um 1 cm überragenden *Milztumors*. Im gleichen Jahre trat ferner *an der Stirn* eine charakteristische *Hautläsion* auf: 1 cm grosse, gelbrote Effloreszenz, aus einer deutlich eingefallenen, etwas abgeblassten zentralen Narbe bestehend, an die sich nach oben und unten halbmondförmige, teils mit squamösen Auflagerungen bedeckte Schwellungen anschliessen. Bei Glasdruck deutlich die gelbbraune Eigenfarbe des Infiltrates erkennbar. Dermatologische Diagnose (Prof. Naegeli, Bern): *Annuläre Form eines Boeckschen Sarkoids* (später durch Probeexzision bestätigt). 1940 wurde von der Halsklinik (Prof. Lüscher) an der *Schleimhaut des Nasenseptums und der untern Muschel* links eine leicht höckerige, histologisch charakteristische Boeckläsion festgestellt. Auch hier konnten weder im histologischen Praeparat, noch durch einen bis heute über zwei Passagen (auch histologisch) verfolgten Meerschweinchenversuch Tb-Bazillen nachgewiesen werden.

Knochensystem: Äusserlich hatte man schon im Jahre 1937 an beiden Zeigefingern eine auffällige, an Spina ventosa erinnernde Schwellung bemerkt. Der radiologische Befund war aber damals noch negativ. Da jedoch die Weichteilveränderungen langsam, aber stetig an Ausdehnung zunahmen, wurden in der Folge mehrfach Kontrollröntgenbilder der Hände und der Füsse angefertigt, die erstmals im Juni 1938 im Bereich

der auffälligsten Weichteilschwellung an einer Zeigefingergrundphalange mehrere unregelmässige Aufhellungen erkennen liessen. Aus diesen Aufhellungen entwickelte sich im Verlauf von 1 ½ Jahren das typisch zystische Bild der Jünglingschen Ostitis, und im weiteren Verlauf kam es zur Ausbildung analoger Veränderungen an zahlreichen Stellen des Hand- und Fusskeletes.

Eine Serum-Kalziumbestimmung im Zeitpunkt der Entwicklung dieser Knochenveränderungen ergab den Wert von 13.4 mg %. Gleichzeitig liess sich im EKG die für das Vorliegen einer Hyperkalzaemie charakteristische Verkürzung der QT-Strecke nachweisen (0.32 Sekunden bei einer Frequenz von 68 anstatt 0.34 — 0.4 Sekunden nach der Tabelle von Holzmänn und Hegglin). 4 Monate später Serum-Kalzium 14.8 mg %, Phosphor 3.85 mg %, Plasmaphosphatase 3.7 Bodansky-Einheiten (normal). Kalziumausscheidung im Urin normal (siehe Tabelle 2). Eine nachträgliche Prüfung verschiedener EKG vom Jahre 1937 zeigte normale Werte der QT-Strecke. Es dürfte demnach damals (vor dem Auftreten der Knochenveränderungen?) ein normaler Kalziumspiegel vorgelegen haben.

Für das Bestehen einer Niereninsuffizienz fand sich bei dem Kranken nie ein Anhalt (spez. Gew. einzelner Morgenurinportionen bis 1029). Albumen negativ, im Sediment mehrfach viele Oxalatkristalle, sonst keine Formelemente. Blutdruck 115—130/75—95.

Epikrise. 25-jähriger, früher gesunder Mann. Nach kurz dauernder fieberhafter Erkrankung tritt hier in 20. Altersjahr ein bis heute schleichend verlaufendes Leiden auf, das vorerst zu einer generalisierten, besonders am Lungenhilus eindrucklichen Lymphdrüsenanschwellung führt. Später traten noch hinzu: ein palpabler Milztumor; eine solitäre annuläre Hauteffloreszenz an der Stirn; eine höckrige, umschriebene Schwellung im Bereiche der Nasenschleimhaut sowie multiple Weichteilschwellungen an Fingern und Zehen nach Art der Spina ventosa; ebendort, jedoch erst wesentlich später nachweisbar, zystische Aufhellungen des Knochens. Die Diagnose des Morbus Boeck wird durch den bioptischen Befund an zwei Lymphdrüsen sowie an den Läsionen der Stirnhaut und Nasenschleimhaut, durch die im bioptischen Material stets negativ verlaufenen Untersuchungen auf Tb-Bazillen und schliesslich durch das Fehlen und später nur bei 1:1000 schwach positive Ausfallen der Tuberkulinreaktion sichergestellt.

Mehrfache Bestimmungen des Serum-Kalziumspiegels ergaben eine deutliche Hyperkalzaemie von maximal 14.3 mg % mit QT-Verkürzung im EKG. Andere Störungen des Mineralstoffwechsels nicht nachweisbar. Ebenso nie Zeichen von Niereninsuffizienz.

3) *Alfred R., geb. 1911.* Diese weitere Beobachtung von Boeckscher Krankheit mit Hyperkalzaemie verdanken wir der medizinischen Klinik, Bern (Prof. W. Frei). Bei dem 29-jährigen auf Tuberkulin stets negativ reagierenden Manne besteht neben einer ausgesprochenen Hilusvergrößerung eine kleinfleckige Verschattung der Lungenfelder, ein Milztumor und eine kleinknotige Konjunktivitis (Probeexzision: subepitheliale Verkalkung und hyaline Degeneration). Später fanden sich auch sehr diskrete subepitheliale Verkalkungen in peripheren Partien der Hornhaut (siehe auch Arbeit Haldimann). Keine Zeichen der Jünglingschen Otitis, ebenso wenig Zeichen der Niereninsuffizienz (spez. Gew. der Tagesurinmenge bis 1025, im Blut Harnstoff-N 21 mg %, Rest-N 26 mg %; Blutdruck 110/60 bis 130/70. Urin: Albumen +, Sediment bei sehr zahlreichen Untersuchungen mehrfach Oxalatkristalle enthaltend). Serumkalziumwert 13.6 mg %, Phosphor 6.8 mg %.

Epikrise. Morbus Boeck mit Schwellung der Hilusdrüsen und kleinfleckiger Aussaat in die Lungenfelder bei einem 29-jährigen Mann. Tuberkulinproben negativ. Palpabler Milztumor. Kleinknotige Konjunktivitis (subepitheliale Verkalkung und hyaline Degeneration) und subepitheliale Verkalkung peripherer Hornhautpartien. Hyperkalzaemie von 13.6 mg %.

Besprechung der Befunde.

Für alle drei Beobachtungen dürfte die Diagnose der Boeckschen Krankheit feststehen. Ein typisches Ergriffensein der Haut liegt zwar nur bei einem der drei Fälle vor. Doch darf diese Tatsache heute, wo wir den Morbus Boeck als generalisierten Krankheitsprozess mit von Fall zu Fall wechselnder Organlokalisation kennen, nicht weiter verwundern. Von Interesse ist aber gerade in dieser Beziehung unsere zweite Beobachtung. Die schon im Jahre 1937 trotz fehlender Hautveränderungen auf Morbus Boeck lautende Diagnose wurde hier zwei Jahre später durch das Auftreten einer typischen solitären Hauteffloreszenz bestätigt. Damit war ein weiteresmal erwiesen, dass eine rein viszerale Form des Morbus Boeck tatsächlich existiert.

In der nachfolgenden Tabelle sind die Werte des *Kalk- und Phosphorstoffwechsels* unserer drei Fälle zusammengestellt. Als einzige konstante Abweichung finden wir eine Hyperkalzaemie. Kalziurie und Blutphosphorspiegel weisen nur geringfügige oder inkonstante Abweichungen auf. Blutphosphatase normal (Fall 1 und 2).

Tab. 2.

Datum.	Kalzium mg %	Phosphor mg %	Phosphatase Bod. E.	Kalziurie mg
<i>Fall 1.</i>				
8. 2. 39.	15.3			
11. 2. 39.	16.3	4.3		
16. 11. 40.	12			
21. 11. 40.	13.6	3.25	4	
19.—21. 11. 40.				175
				207
				233
12. 6. 41.	14.4	5.75		
11. 9. 41.	12.4		5.2	
2. 9. 42.		4.85	2.7	
30. 10. 42.	12.1			
19. 1. 43.	11.2			
<i>Fall 2.</i>				
24. 8. 40.	13.4			
22. 10. 40.	12.1	2.8		
9. — 11. 12. 40.				99
				144
				33
13. 12. 40.	14.8	3.85	3.7	
<i>Fall 3.</i>				
	13.6	6.8		

Von besonderem Interesse sind nun aber die Veränderungen des Kalkhaushaltes im Gewebe. Am eindrucklichsten sind in dieser Beziehung die Befunde des ersten Falles. Neben einer eigenartigen mit Kalkvermehrung einhergehenden, im Röntgenbild wolkig angeordneten Störung des Knochenbaues finden wir hier abnorme Kalkablagerungen in den verschiedensten Organen, so in den Nieren, in der Milz, in der Magenschleimhaut, in den Lymphdrüsen, in Konjunktiva und Kornea, in den Lungen, im arteriellen System und im periartikulären Gewebe. Analoge Verkalkungen finden sich bei Fall 3 in Konjunktiva und Kornea und geringfügige Verkalkungen in den Lymphdrüsen bei allen drei Fällen.

Für all diese Verkalkungsprozesse stellt sich nun die Frage, ob wir es hier mit *echten Kalkmetastasen* im Sinne Virchows (Kalkablagerung im gesunden Gewebe) oder um rein *dystrophische Ver-*

kalkungen (Kalkablagerung im kranken Gewebe) zu tun haben. Eine generelle Entscheidung ist für unsere Fälle nicht möglich, da hier je nach Lokalisation der eine oder der andere Verkalkungsvorgang in Betracht fällt. Von der Milz z. B., deren Kalkgehalt dem Röntgenbild zufolge erheblich vermehrt ist, kann mit Bestimmtheit ausgesagt werden, dass es sich um ein in seiner ganzen Ausdehnung krankhaft verändertes Organ (Boeckherde), somit um eine dystrophische Verkalkung handelt. Vom arteriellen System andererseits, das der Sitz schwerster generalisierter Verkalkungsprozesse ist, können wir mit Sicherheit annehmen, dass nicht eine generalisierte Verkalkung Boeckschen Gewebes vorliegt, da ein so ausgedehntes Ergriffensein des Gefässsystems durch Boecksche Läsionen nicht in Frage kommen kann. Es würde sich demnach hier um echte Kalkmetastasen handeln.

Die Frage metastatische oder dystrophische Verkalkung darf demnach für unsere Fälle nicht in Form einer Alternative gestellt werden, da beide Prozesse nebeneinander vorkommen.

Als rein *dystrophische Verkalkung* betrachten wir die Kalkablagerung in der Milz, in den Lymphdrüsen, in der Konjunktiva und mit grosser Wahrscheinlichkeit auch in den Lungen. Die Lunge ist zwar schon sehr lange als bevorzugtes Kalkmetastasenorgan bekannt. Doch ist in unserem ersten Fall, um den es sich hier handelt, der allmähliche Übergang von der initialen, durch Boeckläsionen bedingten weichfleckigen Aussaat in das Bild der miliaren Kalzinose zu deutlich verfolgbar, als dass eine prinzipielle Trennung von Boeckscher Aussaat und nachheriger Verkalkung angezeigt wäre.

Für die Verkalkungen der *Kornea* scheint eine endgültige Stellungnahme noch nicht möglich zu sein. Haldimann neigt nach kritischer Würdigung der Literatur eher dazu, einen Prozess echter Kalkmetastasenbildung anzunehmen.

Echt *metastatische Verkalkung* dürfte ferner in der Magenschleimhaut, im arteriellen System und im periartikulären Gewebe vorliegen.

Einer besondern Besprechung bedarf das Verhalten der Niere. Auch sie gilt, wie die Lunge, als ausgesprochenes Kalkmetastasenorgan. Die klassische Kalkmetastasenniere, wie wir sie vom primären Hyperparathyreoidismus her kennen (Albrightsche Schule, Anderson, Wernly), ist radiologisch durch herd-

förmig fleckige, in der Anordnung oft den Markpyramiden entsprechende Verschattungen gekennzeichnet. In unserem Fall 1 haben wir es aber mit einer vorwiegend diffusen Verschattung zu tun. Es stellt sich demnach die Frage, ob nicht auch hier, wie in der Lunge, eine sekundäre Verkalkung im Nierengewebe zerstreuter Boeckläsionen vorliegt. Boecksche Erkrankung der Nieren ist bisher klinisch verschiedentlich angenommen worden (Salvesen, Dressler u. a.); pathologisch-anatomische Befunde liegen jedoch nur in sehr geringer Zahl vor, und bei diesen Beobachtungen handelt es sich eher um knotenförmig umschriebene Nierenläsionen (Spencer und Warren, Hollister und Harrell). Eine diffuse Aussaat Boeckscher Herde im Nierenparenchym ist unseres Wissens bisher nur zweimal beschrieben worden. Im Falle Chanials mit typischer Boeckläsion der Haut und der Lungen zeigte die Obduktion eine miliare, sehr dichte knötchenförmige Infiltration beider Nieren durch Boeck-Herde. Ähnliche Verhältnisse finden sich im Falle Stähelins wieder. Klinisch war in beiden Fällen deutliche Albuminurie und mikroskopische Haematurie, bei Chanial ausserdem leichte Azotaemie festgestellt worden. Diese zwei Beobachtungen können nun zwanglos mit unserem ersten Fall in Beziehung gebracht werden. Die von uns gleichzeitig mit dem Aufgehen der miliaren Boeck-Aussaat in den Lungen beobachtete initiale Haematurie und Hypertonie dürften mit der Aussaat in die Nieren zusammenfallen. Die anschliessend einsetzende Niereninsuffizienz ist als Ausdruck einer ausgedehnten Zerstörung des Nierenparenchyms mit sekundärer Schrumpfung des Organes zu deuten. Und schliesslich hat offenbar die Verkalkung der Boeckschen Läsionen zum radiologischen Bilde der diffusen Kalkvermehrung geführt. Wir glauben demnach, dass die Nierenaffektion unseres Falles 1 mit grosser Wahrscheinlichkeit einem mit sekundärer Verkalkung einhergehenden Nieren-Boeck entspricht.

Ob auch für die *Knochenaffektion* eine analoge Deutung (diffuse Aussaat Boeckscher Herde ins Knochenmark und sekundäre Verkalkung) zulässig ist, kann für unsern Fall wohl kaum mit Sicherheit entschieden werden. Eine biopsische Untersuchung konnte infolge Kleinheit des Knochenstückes keine Entscheidung bringen. Immerhin ist diese Möglichkeit nach den Befunden der Sternalpunktion (Dressler) und nach unsern heutigen Kenntnissen über die Ausdehnung und über das Wesen der Jünglingschen Ostitis

nicht ohne weiteres von der Hand zu weisen. Für eine solche Annahme würde u. a. auch die Tatsache sprechen, dass bei diesem Fall kleinknotige Dissemination auch in andere Organe stattgefunden hat (Lungen, Milz, Lymphdrüsen; Nieren (?)).

Literatur.

Ähnliche Störungen des Mineralhaushaltes bei Boeckscher Krankheit sind in der Literatur bisher zweimal beschrieben, 1939 durch Harrell und Fisher und 1941 durch v. Creveld. Daneben wird neuerdings auch von ophthalmologischer Seite über Hornhautverkalkungen beim Morbus Boeck berichtet (Seefelder, Vogt; Haldimann in seiner Bearbeitung unseres ersten und dritten Falles).

Harrell und Fisher fanden bei 10 Fällen von Boeckscher Krankheit, deren Blutkalkwerte sie z. T. über längere Zeit verfolgten, sechsmal eine eindeutige Hyperkalzaemie. Auffällig sind auch hier, wie bei unsern eigenen Beobachtungen, die beträchtlichen Schwankungen der Kalziumwerte teils in grösseren Zeiträumen, teils aber auch schon im Verlauf von 2 Tagen (14.2 und 13.0; 14.1 und 14.8 mg % je im Abstand von zwei Tagen). Der Blutphosphorspiegel zeigte keine eindeutigen Abweichungen von der Norm, während die angegebenen Phosphatasewerte nach Ansicht der Autoren als leicht erhöht zu betrachten sind. Pathologische Gewebsverkalkungen, insbesondere auch Verkalkungen des Nierenparenchyms oder Nierensteine, nach denen gesucht wurde, konnten nicht festgestellt werden.

Analoge Verhältnisse der Blutwerte finden sich in 5 unter 6 Fällen v. Crevels. Auch hier sind bedeutende zeitliche Schwankungen des Kalziumspiegels zu verzeichnen. Von besonderem Interesse ist das in dieser Arbeit zweimal erwähnte Vorkommen von Nierensteinen: bei Fall 1, einem 14-jährigen Mädchen mit leichter Hyperkalziurie, Osteoporose und einem operativ nachgewiesenen Oxalatstein, bei Fall 4 mit radiologisch gesicherter Nephrolithiasis. In einem weiteren Fall derselben Arbeit werden periartikuläre Verkalkungen verzeichnet, die, soweit aus der Abbildung ersichtlich, mit denjenigen unserer ersten Beobachtung übereinstimmen. Ein wesentlicher Unterschied der zwei Fälle liegt jedoch darin, dass bei dem betreffenden Falle v. Crevels gleichzeitig Osteoporose, in unserem Fall aber eine Kalkvermehrung des Skeletes vorliegt.

Tab. 3.

	Kalzium mg %	Phosphor mg %	Phosphatase Bod. F.
<i>Harrell und Fisher</i>			
Fall 2 (1936)	11.1	3.8	
Fall 3 (1936—38) ..	9.6; 14.2; 13.0; 14.2	3.7; 3.7; 3.0; 3.0	5.7; 8.5; 6.7
Fall 4 (1937—38) ..	12.8; 10.7	3.6; 2.5	4.9
Fall 7 (1938—39) ..	9.1; 11.2	3.0; 3.3	4.4
Fall 8 (1938)	14.1; 14.8	3.7; 3.6	7.4
Fall 10 (1939)	12.6; 12.6	4.5	7.3
<i>Van Creveld</i>			
Fall 1 (1939—40) ..	15.6; 15.0; 13.3; 10.9	3.7	2.9
Fall 2 „ „ ..	12.3	3.9	4.3
Fall 4 „ „ ..	14.1		
Fall 5 „ „ ..	10.5; 14.5	3.0; 2.0	
Fall 6 „ „ ..	14.0		
Normalwerte	10—11	3—4	2—5 (für Erwachsene)

Diskussion der möglichen Entstehungsbedingungen.

Eine befriedigende Erklärung des vorliegenden Syndroms von Hyperkalzaemie mit Organverkalkungen bei Morbus Boeck kann bis heute nicht gegeben werden, da z. T. die nötigen klinischen Befunde, hauptsächlich aber die pathologisch-anatomischen Unterlagen noch fehlen. Immerhin glauben wir aber, bei der Besprechung dieser Frage zwei Momente in den Vordergrund stellen zu müssen: einmal das häufige Ergriffensein des Knochenmarkes und damit auch des Knochens bei Boeckscher Krankheit (Jünglingsche Ostitis), woraus sich eine Einwirkung auf den Kalkhaushalt vom Skelet aus ergeben würde, und in zweiter Linie das Vorhandensein einer schweren Niereninsuffizienz in unserem eindrucklichsten Fall Nr. 1, die andererseits auf eine Störung des Kalkstoffwechsels nach Art der renalen Ostitis hindeuten könnte.

Neben diesen beiden pathogenetisch sicher bedeutungsvollen Faktoren sind für das vorliegende Syndrom noch zwei andere Möglichkeiten der Erklärung in Betracht gezogen worden (Harrell und Fisher, v. Creveld). In Übereinstimmung mit den betreffen-

den Autoren halten wir jedoch beide Annahmen für unzutreffend, weshalb sie an dieser Stelle nur kurz erwähnt werden sollen.

Die Hyperkalzaemie unserer Fälle könnte mit der bei Morbus Boeck häufig beobachteten *Hyperproteinaemie* in Zusammenhang stehen (Vermehrung des an die Bluteiweisskörper gebundenen Kalkes). Gegen diese Auffassung spricht, dass in unsern eigenen wie in den Fällen der Literatur bisher bei längerer Beobachtungszeit ein Parallelgehen der beiden Werte nie festgestellt werden konnte. Dazu kommt, dass die Hyperproteinaemie des Morbus Boeck auf einer Vermehrung der Globuline beruht, nicht aber auf einer Zunahme der kalkbindenden Albuminfraktion. Überdies muss die in unserem Fall 2 festgestellte Verkürzung der QT-Strecke im EKG auf einer Vermehrung des jonisierten Blutkalkes beruhen, da nur dieser Kalkfraktion, nicht aber der eiweissgebundenen eine derartige Wirkung zukommt (vgl. Wuhrmann und Leuthardt, Pinösch).

Auch einen Hyperparathyreoidismus als Ursache von Hyperkalzaemie und Organverkalkung müssen wir ablehnen. Eine Boeck-Läsion in den Epithelkörperchen würde als destruierender Prozess die Organfunktion vermindern und nicht steigern. Ein *koexistieren-der primärer Hyperparathyreoidismus* durch Adenombildung in den Epithelkörperchen kann schon wegen der Seltenheit eines solchen Vorkommens nicht in Betracht gezogen werden. Zudem findet sich beim primären Hyperparathyreoidismus — von gewissen durch Niereninsuffizienz komplizierten Fällen abgesehen — neben der Hyperkalzaemie stets eine deutliche Senkung des Blutphosphorspiegels, die nun aber bei allen eigenen und bei den Beobachtungen der Literatur gerade vermisst wird. Eine Vermehrung der schattengebenden Kalksubstanz des Skeletes, wie sie in unserem Fall 1 vorliegt, gehört überdies nicht zum Bilde des primären Hyperparathyreoidismus und ist bei diesem bisher nie beschrieben worden. Die Organverkalkungen dieses gleichen Falles stimmen nach Lokalisation und Art in keiner Weise mit den Kalkmetastasen des primären Hyperparathyreoidismus überein (vgl. oben die Besprechung der Nierenverkalkung).

Dagegen muss die Möglichkeit einer renal bedingten Kalkstoffwechselstörung, jedenfalls für unseren ersten Fall in Erwägung gezogen werden. Das Krankheitsbild der *renalen Ostitis* (renale Rachitis, renaler Zwergwuchs, renaler Hyperparathyreoidismus),

welches hier in Frage steht, ist durch eine generalisierte, mit stark vermehrtem Knochenumbau einhergehende, histologisch dem primären Hyperparathyreoidismus entsprechende Osteopathie gekennzeichnet und wird bei Zuständen lang dauernder Niereninsuffizienz beobachtet. Im Gegensatz zum primären Hyperparathyreoidismus sind bei der renalen Ostitis aber auch Beobachtungen gemacht worden, die im histologischen Bild des gesteigerten Knochenumbaus ein Überwiegen des Neuanbaues erkennen lassen (Rutishauser und Mach, Fall 5) und somit einen vermehrten Kalkgehalt des Skeletes aufweisen wie unser Fall 1, der im übrigen auch Kalkmetastasen zeigt, die nach Art und Lokalisation eine grosse Ähnlichkeit haben mit den Organverkalkungen anderer in der Literatur beschriebener Fälle von renaler Ostitis (Shelling und Remson, Schellack, Albright).

Trotz der weitgehenden Übereinstimmung dieses einen Falles mit dem Bild der renalen Ostitis glauben wir aber, eine generelle Entscheidung der ätiologischen Frage in diesem Sinn für das vorliegende Syndrom nicht annehmen zu dürfen. Denn einmal wird bei den meisten hier wiedergegebenen Fällen (eigene Fälle 2 und 3, Mehrzahl der Fälle v. Crevelds, Harrels und Fishers) eine chronische Niereninsuffizienz vermisst. Im weitern gehört auch zum klinischen Bild der renalen Ostitis im allgemeinen nicht die Hyperkalzaemie, sondern eine leichte Senkung des Blutkalkspiegels bei deutlich ausgeprägter Hyperphosphataemie. Wir möchten demnach annehmen, dass in unserem ersten Fall die Niereninsuffizienz nicht die einzige Ursache der Kalkstoffwechselstörung darstellt, dass sie aber vielleicht doch dazu beiträgt, eine aus anderer Ursache entstandene Veränderung im Kalkstoffwechsel wesentlich zu unterstützen, und dass möglicherweise erst durch das Zusammenwirken zweier gleichgerichteter pathogener Vorgänge ein so ausgeprägtes Krankheitsbild sich ergeben könnte.

Die primäre Ursache der Kalkstoffwechselstörung glauben wir mit viel grösserer Wahrscheinlichkeit im Skelet suchen zu dürfen. Eine Einwirkung von Skeleterkrankungen auf den allgemeinen Kalkstoffwechsel, im besondern auf den Nebenschilddrüsenapparat, ist aus zahlreichen Beispielen bekannt. So findet sich u. a. eine diffuse Epithelkörperchenhyperplasie bei der Osteomalazie und der Rachitis, bei seniler Osteoporose, Myelom, metastatischer Knochenmarkskarzinose, bei Spruetetanie und experimenteller Gallengangs-

fistel mit Osteoporose (Lit. siehe bei Wernly). Verschiedene der hier angeführten Erkrankungen können mit einer geringfügigen, mitunter aber auch mit einer beträchtlichen Hyperkalzaemie einhergehen.

Wenn wir nun auch die Jünglingsche Ostitis in den Rahmen dieser Skeletaffektionen bringen wollen, so erwachsen dieser Annahme zunächst gewisse Schwierigkeiten. Die Jünglingsche Ostitis, die wir heute im allgemeinen als Boeck-Manifestation aufzufassen berechtigt sind, wurde bisher zumeist als eine sehr unscheinbare, nur an bestimmten Praedilektionsstellen des Hand- und Fusskeletes vorkommende Knochenaffektion betrachtet, von der eine Beeinflussung des allgemeinen Mineralhaushaltes wohl kaum erwartet werden könnte. Neuere Beobachtungen haben aber gezeigt, dass die Jünglingschen Knochenveränderungen keineswegs immer in einer so streng lokalisierten Form aufzutreten pflegen. Entsprechende, z. T. sehr grosszystische Veränderungen, die verschiedentlich auch autoptisch und bioptisch als typisch erkannt werden konnten, sind seither in der Literatur sozusagen an allen Teilen des Skeletes beschrieben worden. So stellten Jordon und Osborne bei einem jungen Neger neben ausgedehnten Läsionen des Hand- und Fusskeletes weitere, z. T. sehr grosse zystische Aufhellungen in Humerus, Radius, Ulna, Femur, Tibia und Fibula fest. Ein weitgehend analoger Fall wurde von Longcope und Pierson beschrieben. Mehrfach wird sodann über ein Mitergriffensein eines oder mehrerer Wirbel berichtet (Nickerson; Hollister und Harrell). Nielsen erwähnt einen Fall, bei dem eine grosse Aufhellung im Stirnbein durch Biopsie als Boeck-Laesion erkannt werden konnte. Aber auch im Nasenbein und den Kieferknochen wurden von anderen Autoren entsprechende Veränderungen gefunden. Bei einem Fall Dresslers gelang es, die vorher unsichere Diagnose der Boeckschen Krankheit durch den Nachweis typischer Knötchen im Sternalpunktat zu erhärten.

Diese Beobachtungen der Literatur zeigen uns, dass Boeck-Gewebe praktisch in allen Teilen des Skeletes vorhanden sein kann. Doch ist ein generelles Auftreten Jünglingscher Läsionen noch in einer andern Form möglich, die sich im Röntgenbild sehr viel diskreter anzeigt und anatomisch in einer diffusen, die Knochensubstanz nur sehr wenig beeinflussenden Infiltrierung des Knochenmarkes besteht. Über derartige Fälle, die radiologisch ausschliesslich eine

diffuse Osteoporose des Hand- und Fusskeletes aufweisen, wird von Snapper berichtet. Sehr schön werden ferner diese Verhältnisse einer rein osteoporotischen Form Jünglingscher Ostitis auch durch Beobachtungen illustriert, bei denen dem Auftreten einzelner Zysten ein während Jahren radiologisch kaum erkennbares Stadium leichtester Osteoporose vorausging (Kissmeyer, eigene Beobachtung 2). Von hohem Interesse sind schliesslich in diesem Zusammenhang die pathologisch-anatomischen Untersuchungen Schaumanns, aus denen mit Deutlichkeit hervorgeht, dass schwere Infiltrierungen des Knochenmarkes durch Boeck-Gewebe auch bei normalem oder kaum merklich verändertem Knochen vorhanden sein können.

Aus all diesen Beobachtungen geht hervor, dass die Jünglingsche Ostitis viel häufiger als bisher wohl angenommen wurde, in ausgedehnter Weise das Skelet ergreifen kann. Die radiologischen Veränderungen sind hierbei oft nur äusserst gering und an den grossen Knochen in den meisten Fällen überhaupt nicht zu erkennen. Die Einwirkung einer generalisierten Knochenmarkserkrankung auf den allgemeinen Kalkstoffwechsel hängt nun sehr wesentlich von der Ausdehnung und von der momentanen Aktivität des Krankheitsprozesses ab. Leider entgehen aber diese beiden Faktoren einer direkten klinischen Beobachtung fast vollständig. Wir dürfen aus diesem Grunde bei negativem radiologischem Befund keineswegs die Anwesenheit einer Jünglingschen Ostitis verneinen. So ist es denn auch nicht möglich, für jeden einzelnen der hier wiedergegebenen Fälle das Vorhandensein oder das Fehlen einer Knochenläsion zu bestimmen.

Wenn nun die radiologische Untersuchung des Skeletes eine allgemeine Beurteilung des Knochen-Boeck nicht zulässt, so müssen wir aber doch vermuten, dass gerade im Verhalten des Blutkalkspiegels und vielleicht auch der Blutphosphatase ein indirektes Zeichen gegeben ist, das uns einen tieferen Einblick in die Verhältnisse des Knochensystems erlaubt. Ein strikter Beweis für diese Annahme ist allerdings, bei der Unvollkommenheit der klinischen Untersuchungsmethoden, nicht möglich. Doch scheinen uns gerade auch die periodischen Schwankungen des Blutkalkwertes eine sehr schöne Parallele zu den periodischen Aktivitätsschwankungen der Boeckschen Krankheit zu ergeben, wie sie vor allem vom Lungen-Boeck her bekannt sind (v. Creveld, Dressler).

Wir möchten demnach annehmen, dass die Hyperkalzaemie und die Organverkalkungen unserer Fälle mit Wahrscheinlichkeit auf einen klinisch nicht immer nachweisbaren Knochen-Boeck zurückzuführen sind. Im Hinblick auf unsern ersten Fall sei noch einmal hervorgehoben, dass uns eine generalisierte Boeckerkrankung des Knochenmarkes mit sekundärer Verkalkung und Vernarbung der Läsionen sehr wohl möglich erscheint. Doch dürfte eine sichere Unterscheidung gegenüber einer renalen Ostitis in diesem Falle wohl kaum möglich sein.

Zusammenfassung.

Die vorliegende Arbeit bringt anhand von drei eigenen und 11 weiteren Fällen der Literatur die Beschreibung eines bei Morbus Boeck gelegentlich vorkommenden Syndroms, das durch die Anwesenheit einer Hyperkalzaemie mit Organverkalkungen charakterisiert wird. Als eindrucklichstes Beispiel dieser Serie sei unsere erste Beobachtung erwähnt, bei der sich neben den Veränderungen einer generalisierten Boeckschen Krankheit eine Hyperkalzaemie von 16.3 mg % vorfand, ferner Organverkalkungen in Lungen, Magen, Nieren, sämtlichen Arterien, Lymphdrüsen, Milz, Konjunktiva, Kornea, Trommelfellen und im periartikulären Gewebe, sowie schliesslich eine eigenartige, mit Kalkvermehrung einhergehende Skeletaffektion. Bei den Organverkalkungen dieses Falles dürfte es sich z. T. um dystrophische Verkalkungen im Bereiche der Boeckschen Läsionen, z. T. aber auch um echte Kalkmetastasen im Sinne Virchows handeln.

Hinsichtlich der Genese dieser Hyperkalzaemie ist, wie gezeigt wurde, eine einheitliche Stellungnahme noch nicht möglich. Eine Beziehung der Blutkalkvermehrung zu der bei Boeckscher Krankheit oft vorliegenden Hyperproteinaemie wurde abgelehnt, ebenso der auf der Annahme eines koexistierenden primären Hyperparathyreoidismus beruhende Erklärungsversuch. Dagegen erscheint es als durchaus möglich, dass die Störung im Kalkstoffwechsel durch ossäre Boeckläsionen bedingt ist, die, allerdings oft dem klinischen und sogar radiologischen Nachweis entzogen, nach unserem heutigen Wissen auch generalisiert auftreten können. Für gewisse Fälle, insbesondere für unseren ersten Fall, mag ausserdem das

gleichzeitige Mitbestehen einer chronischen Niereninsuffizienz (Kalkniere) pathogenetisch von Bedeutung sein. — Aus praktisch diagnostischen Erwägungen wird empfohlen, bei allen mit Boeck-scher Krankheit Befallenen periodisch den einfach durchzuführenden Sulkovitch-Test im Urin vorzunehmen.

Nachtrag.

Während der Drucklegung dieser Arbeit bot sich uns Gelegenheit, als weitem hierhergehörenden Fall für kurze Zeit einen 24j. Mann, Hans K., zu beobachten, der im Juni 1943 bei völlig ungestörtem Allgemeinbefinden und gutem Allgemeinzustand wegen einer bereits 3 Monate bestehenden Keratitis in die Berner Augenklinik (Prof. Goldmann) gewiesen worden war. In Zusammenarbeit mit dieser Klinik ergaben sich die folgenden Befunde:

Keratitis und kleinknötchenförmige Iritis des linken Auges. Beid-seitige derbhöckrige Schwellung der Ohrspeicheldrüsen und palpatorisch feststellbare Schwellung der Unterkieferspeicheldrüsen. Palpabler Milz-tumor und generalisierte Lymphdrüsen-schwellungen, daneben beid-seitige Hilusvergrößerung mit netzförmig seinfleckigen Lungenschatten, hauptsächlich in den Mittelfeldern. Mantoux 1 : 10,000 negativ. Biop-tischer Befund aus der Ohrspeicheldrüse und einer kubitalen Lymphdrüse: Epitheloidzellknötchen mit spärlichen Langhans'schen Riesenzellen ohne Verkäsung. Serumkalziumspiegel (zu verschiedenen Zeiten in 3 Laboratorien untersucht) 16.3—16.8 mg %. Phosphor 3.8 mg %, Phosphatase 3.2 Bod.E. Hyperkalziurie mit positivem Sulkowitch-Test (milchige Trübung). Hand- und Fussknochen, sowie Abdomenleeraufnahme o.B. Sternalpunktat o.B.

Übrige Laboratoriumsbefunde: Urin: Spur Albumen, spez. Gew. bis 1,025, im Sediment einige Leukozyten und Erythrozyten, sowie Oxalat-kristalle. Hgb. 108%, Leukozyten 8,200, davon 10.5 % Monozyten, sonst o.B. Senkungsreaktion 60 und 87 mm nach 1 und 2 Std. Serum: Gesamt-eiweiss 9.53 %, Albumin 2.96 %, Globulin 6.57 %, Alb/Glob 0.45. Harn-stoff 91.2, später 76.8 mg %.

Diagnose: Morbus Boeck mit Herfordtschem Syndrom; Lokalisation in Hornhaut, Iris, Speicheldrüsen, Lymphdrüsen, Milz und Lungen. Hyperkalzaemie mit fraglicher partieller Niereninsuffizienz, ohne radiologisch nachweisbare Skeletaffectio.

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REVUE DES LIVRES.

Ben Karpman: Case Studies in the Psychopathology of Crime (The Mental Sciences Publishing Co., New York, Washington, Chicago 1933). 1042 pp. quarto in 2 Vol.

These two mastodont volumes contain 5 (I) case studies of criminals, each comprising between 154 and 306 pages. In the preface the author points out that as the book is addressed mainly to a public that has no direct interest in refined psychiatric diagnosis and intimate psychiatric discussion such interpretations have in the main been omitted. Thus the epicritical discussions or the epitomes are astonishingly poor, varying between 1 and 2 $\frac{1}{4}$ pages. This makes a strange disproportion between the ample life histories given and the critical scientific interpretations. Besides the materials of the life histories are mainly composed of auto-biographical notes by the patients themselves and letters, completed by descriptions of the curricula of the subjects. While the life records are very detailed and complete there are few medical observations on the morphological and constitutional make-up of the subjects.

It is a pity that the great work involved in the collecting of all these materials has not been completed with a more penetrating investigation of the constitutional and pathological factors that have produced the criminal behaviour, and been integrated with a diagnostical, medical and criminological analysis of the rich raw materials given.

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The determination of oxygen saturation in small amounts of blood, by means of the Pulfrich step photometer.

By

Dr. J. H. P. JONXIS.

(Submitted for publication July 12, 1943).

Some years ago (1) I published a method for the determination of the oxygen saturation in small amounts of blood by means of the Pulfrich Step Photometer. Since then I made some improvements, so that the mercury lamp is no longer necessary and it can be done by means of the normal equipment of the Pulfrich Step Photometer. The principle is still the same and has been described in the paper of Brinkman and Wildschut (2). The extinction of the haemoglobin solution is determined by using the Pulfrich filter S. 61. A glance on the extinction curves of Hb and HbO₂ will show that this filter is very well suited for measuring the differences between Hb and HbO₂.

Fig. 1 is the experimental proof of the direct proportionality between the percentages of haemoglobin, resp. oxyhaemoglobin, and the extinction, filter S. 61 being used. It shows at the same time the difference in the extinction by fully reduced and fully oxygenated blood, in relation to the total haemoglobin concentration. If, for instance, the extinction of a 14.0 p.c. haemoglobin solution in the reduced state is found to be represented by the point D, its corresponding oxygenation extinction must have the value E, and any partial saturation will be indicated by linear

interpolation between D and E. F represents the extinction of a 14.0 p.c. haemoglobin solution, partly saturated with O_2 . The concentration of Hb and HbO_2 in this solution will be proportional to DF and FE.

It will be clear now that a determination of the percentage oxygen saturation may be effected by two consecutive measurements of extinction, first on the original sample and then on the corresponding reduced sample. The extinction of the completely oxygenated sample can be calculated from that of the reduced one.

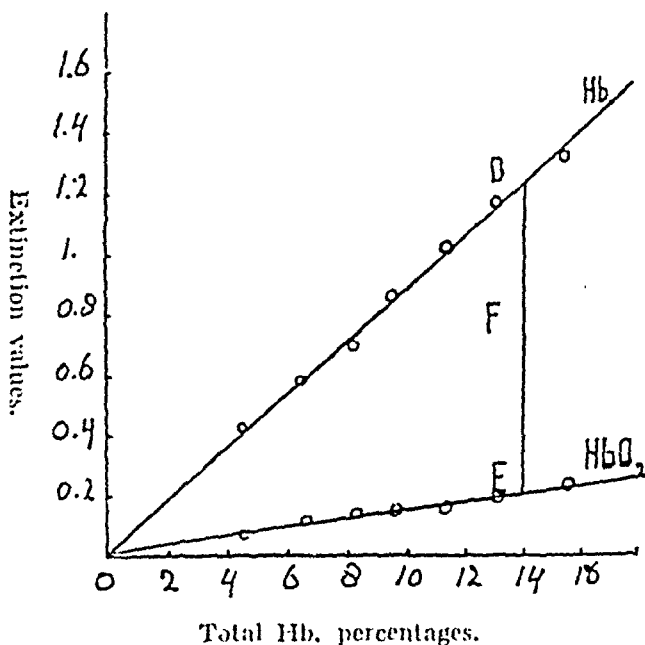


Fig. 1. Relation of the extinction by Hb and by HbO_2 , as read from the stepphotometer to haemoglobin percentage, for 1 mm. layer. Pulfrich filter S61.

The advantages of using the reduced state for the estimation of total haemoglobin have been exposed in the communication by Brinkman and Wildschut.

Taking of the bloodsample.

The hand is kept in water of 44 degrees C. for 5 minutes. The capillary blood is then fully arterialized. A small glass vessel with a pointed bottom (f. i. the lid of a weighing bottle or a small stoppered funnel) is completely filled with pure paraffine oil. The hyperaemised finger is well punctured by vaccinostyle and the vessel with paraffine oil is immediately kept against the wound,

so that the blood is flowing freely under the oil and collects at the bottom. In half a minute an amount of about 0.5 cm³ of blood must have been obtained, otherwise the contact with paraffine oil may be too intensive. The blood is then at once drawn up into a small syringe. We use an allglass syringe of 0.5 cm³, a small needle cemented on it. The syringe also holds a very small gold- or lead globule for mixing purposes. The dead space of the syringe has previously been filled with a concentrated clear saponine solution. Airbubbles have carefully to be avoided.

The blood in the syringe is haemolysed by shaking. Now the cuvette (Pulfrich cuvette 1 mm.) is filled with the haemolysed blood. The first drops from the syringe are not to be used. Owing to the high viscosity of the haemolysed blood the contact of the haemoglobin with the air is very small and is limited to the upper layer. The cuvette is filled completely and immediately closed. Now the first photometric reading is made. Then the haemoglobin in the cuvette is completely reduced by adding some cristalls of sodium hydrosulphite. The solution is carefully mixed with a small glassrod. Then the extinction of the reduced sample is determined. The cuvette is thoroughly cleaned afterwards, so that there is no chance of the original sample being contaminated by traces of sodium hydrosulphite.

Calculation of the percentage oxygen saturation from 2 extinction values.

From fig. 1 it may be deduced that for a given concentration of haemoglobin the quotient of the extinction values for the reduced and oxygenated states amounts to 6.1.

So if the extinction of the original sample is found to be E_s , and that of the reduced sample is E_r , the percentage oxygen saturation will be

$$\frac{(E_r - E_s) 100}{E_r - \frac{E_r}{6.1}}.$$

The accuracy of this method is chiefly

determined by the way in which the bloodsample is taken.

The determination of the extinction values can be made with an accuracy of about 0.02 units, for Hb concentrations, not exceeding 20 p.c., in layers of 1 mm. thickness. This will give a maximal fault in the oxygen percentage of about 3 %.

When the serum is very cloudy there will be an additional extinction. This can be avoided by filling the compensation cuvette (normally filled with water) with a mixture of one part physiological salt solution, one part of the serum and a drop of the concentrated saponine solution.

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Location of the peripheral electrode in precordial leads.

By

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(Submitted for publication July 8, 1943).

When the American Heart Association and the Cardiac Society of Great Britain and Ireland in 1938 suggested a standard technique (11) for electrocardiography with precordial derivation, no decisive stand was taken on the location of the peripheral, so-called indifferent, electrode. It was suggested to place this electrode on the right arm or left leg, preferably the latter, »until it has been established that the former (right arm), which is somewhat more convenient, is equivalent to the latter for all practical purposes or yields results of equal value».

This point has not been settled yet, as some authors think that precordial leads with the peripheral electrode on the right arm — which in the following will be designated as CR (chest-right) — are more suitable, while others prefer derivation with the peripheral electrode on the left leg — CF (chest-foot). Finally, derivation with the peripheral electrode placed on the left arm — CL (chest-left) — has been discussed too though without attracting particular interest.

Kaj Larsen (4, 10) prefers CR, among other reasons, because this derivation in normal subjects shows more constant features than CF: always positive P and positive T, whereas CF may show

positive, diphasic or negative P and, in parasternal leads, occasionally, negative T. Further, CR is stated to give greater deflections than CF.

Deeds & Barnes (2), basing their opinion on the findings in 100 normal subjects, mention several advantages offered by the employment of CR, namely: with this derivation only one lead has to be moved in order to take a precordial electrocardiogram after employment of the extremity leads, whereas two leads have to be moved for CF; further, that CR usually has a positive P, never inverted T, and also a larger R, larger T and smaller RS-T deviation than CF. Finally, it has been the experience of these authors that with the employment of CR it is easier to keep the isoelectrical level constant than on employment of CF.

Taking 400 electrocardiograms on 349 patients with heart lesions, Geiger (3) found IVR (IV: ictus) and IVF to be of the same value in 84 % of the cases, while IVF gave more information than IVR in 13.7 % of the cases, and IVR better information than IVF only in 2.3 % of the cases. Hence the author recommends IVF for routine derivation.

The problem here involved may be tackled, as done by Wolferth & Wood (13) in a more rational manner by employment of the relations between precordial leads and extremity leads.

According to Einthoven, with the ordinary connection of leads the algebraic sum of simultaneous deflections in Leads I and III is equal to the synchronous deflection in Lead II, that is,

$$\text{Lead II} = \text{Lead I} + \text{Lead III}$$

or more briefly $\text{II} = \text{I} + \text{III}.$

This relation holds true and is independent of Einthoven's hypothesis, that the heart is of minimal extension and situated in an electrically homogeneous medium, and that the extremity leads are connected with this medium at the points of an equilateral triangle. The relation merely expresses that the difference in the electrical potential (in electrocardiography often designated as the voltage) between two points a and b should turn out to be the same whether it is measured directly or by addition of the differences in voltage between a and c and between c and b, that is, an entirely physical relation. Consequently, the relation is valid for any system of 3 derivations irrespective of the location

of the three points of derivation. In carrying out this measuring, care must be taken to have the polarity of the galvanometer (electrocardiograph) so that the same clamp is placed at point a when the potential over a-b and the potential over a-c are measured, and that the clamp placed at point b when the potential over b-c is measured is the same as is first placed at point a, while the clamp at point c is kept here.

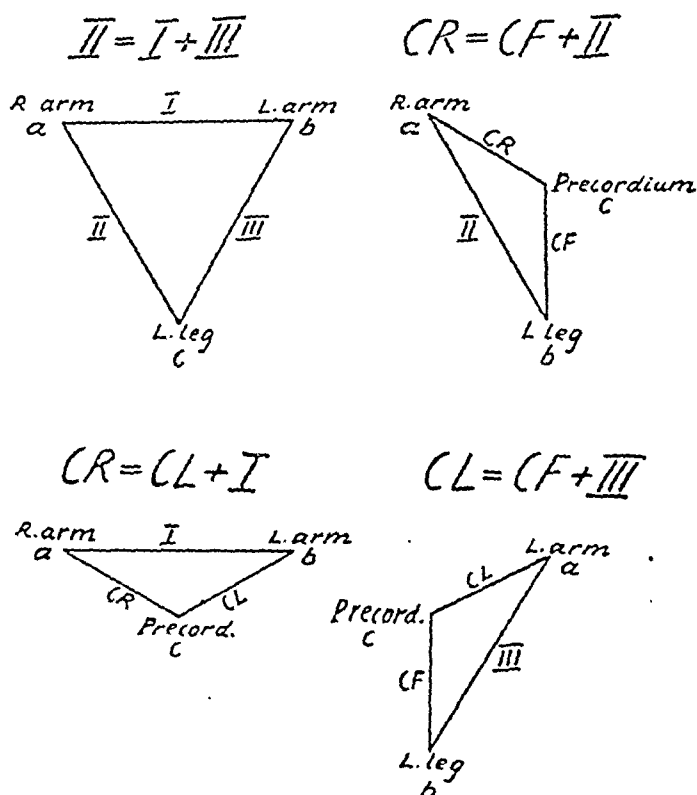


Fig. 1. Diagram of the connection of leads for electrocardiography with derivation from the extremities and with varying combinations of two precordial leads and one extremity lead. The connection of the leads is indicated by the letters a, b and c.

As to the polarity of the electrocardiograph the extremity leads comply with *Einthoven's rule*: that a difference in potential has to be registered by an *upward* deflection if the right arm is *negative* in relation to the left (Lead I) or the left leg (Lead II) and if the left arm is *negative* in relation to the left leg (Lead III). The precordial leads comply with a rule established by Larsen & Warburg (5) and accepted by the American Heart Association and by the Cardiac Society of Great Britain and Ireland: that a dif-

ference in potential between the precordium and some other point has to register as an *upward* deflection if the precordium electrically is positive in relation to the other point.

By placing one electrode over the precordium and the other two on one extremity each, electrocardiograms can be taken simultaneously in various combinations of two precordial leads and one extremity, with employment of connection of leads given in Fig. 1.

Accordingly, in analogy with the relation $II = I + III$, it is possible to set up the diagrams in Fig. 1 and derive the following relations:

$$CR = CF + II$$

$$CR = CL + I \text{ and}$$

$$CL = CF + III.$$

Knowing a set of simultaneous deflections in the extremity leads (or merely their proportionality) and substituting them in the equations above, it is easy to see with which precordial derivation the corresponding deflection is greatest or least. Looking into this relation for various combinations of simultaneous deflections in the extremity leads, it will be found that the corresponding greatest or least deflection in some cases is obtained by employment of CR, in others with CF, and in others with CL. Wolferth & Wood (13) have tabulated various combinations of simultaneous deflections in extremity leads, and from this table it is practicable to read in which precordial lead the corresponding deflection is greatest or least.

A more surveyable picture is obtained if the three variable extremity deflections are replaced by a single variable. As is well known, any set of simultaneous deflections in the extremity leads may be characterized precisely by an electrical vector, the angle of which with the horizontal (Lead I) after Einthoven is called α . Einthoven designated the angles between 0° and 180° in the direction of the clock as positive and gave a negative sign to the angles between 0° and 180° in the opposite direction. The situation of the angles is shown in Fig. 2 — modified after Wenckebach & Winterberg (12) and Carter, Richter & Green (1).

Now it is easy from simple geometrical considerations — as done, for instance, by Wenckebach & Winterberg (12), Pardee (8) and Sabena (9) — for any value of angle α to determine the propor-

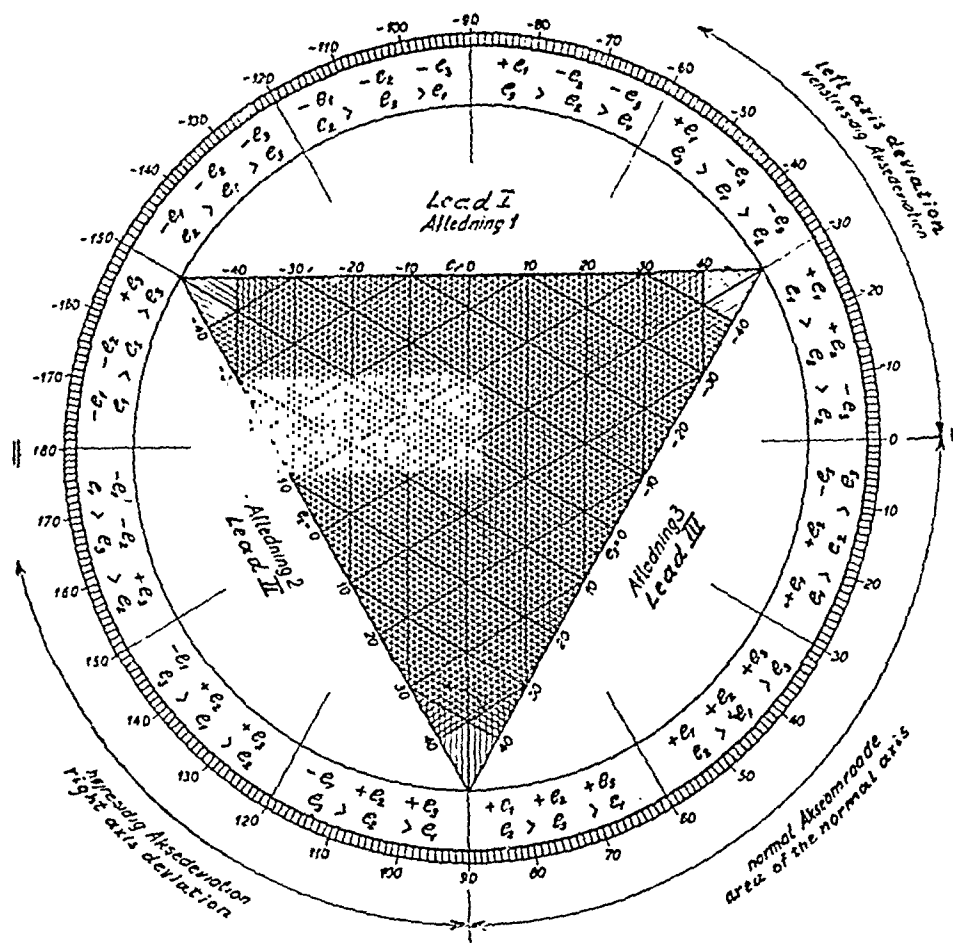


Fig. 2. Diagram, modified after Wenckebach & Winterberg and Carter, Richter & Green, showing the correspondence between various values for angle α and the deflections in the extremity leads.

tionality between the simultaneous deflections in the extremity leads corresponding to this angle. Fig. 2 illustrates this correspondence between the angles and the various combinations of simultaneous deflections. Then by employment of the formulæ above, it is easy to decide which precordial lead will give the greatest or least corresponding deflection.¹ When calculations are carried out for all the values of angle α the following result is obtained (Pardee, 8):

The greatest (*i.e.*, most positive or least negative) deflection is obtained with CR when α is between -30° and $+90^\circ$, with

¹ These considerations are independent of whether or not Einthoven's hypothesis be correct, even though the angle in the latter case has a considerably greater symbolic significance than imagined by Einthoven.

CL when α is between $+90^\circ$ and -150° , and with CF when α is between -150° and -30° .

The least (*i.e.*, least positive or most negative) deflection is obtained with CR when α lies between $+150^\circ$ and -90° , with CL when α lies between -90° and $+30^\circ$, and with CF when α lies between $+30^\circ$ and $+150^\circ$.

From the above it is evident that none of the three leads—CR, CF or CL — will in every instance give greater or smaller deflections than the two others, and consequently none of them can be characterized as the most suitable for every purpose. Within its own particular field each derivation is more suitable than the others.

If we still wish to employ only one of Leads—CR, CL and CF as routine derivation there is no other choice but to realize for which purpose the precordial leads are employed and then select the one most serviceable for the given purpose.

According to the literature and our own experiences there can be no doubt whatever that the practical significance of precordial leads is associated in particular with the diagnosis of cardiac infarction. In comparison hereto, the practical value of these derivations in other fields is relatively slight, and hence it will be reasonable for routine derivation to choose the lead most suitable for the diagnosis of cardiac infarction.

For the present we will leave CL out of consideration and discuss only CR and CF—the subject of the standing dispute. The discussion can be conducted most easily on the basis of the relation

$$CR = CF + II,$$

from which it is obvious that the changes in Lead II are decisive of the relation between the deviations in CR and CF.

In *anterior wall infarction* the typical RS-T and T changes in precordial leads are elevation of RS-T in the acute stage and a subsequent development of a negative T. In Lead II the changes are not constant; in the acute stage an elevation of RS-T may be seen or, less frequently, a depression of RS-T, and T_2 may be inverted or remain positive. In the former case CR gives a higher elevation of RS-T and a deeper inversion of T than are obtained

with CF, in the latter the converse takes place. A great many anterior wall infarcts, however, especially in the chronic stage, give no specific changes in the extremity leads; and it is important to keep in mind that it is just in these cases that precordial leads are of great practical value. In these cases the extremity electrocardiograms show either no abnormality or unspecific changes, most often left axis deviation. As to Lead II in particular, most often there is no deviation of RS-T and T_2 is most frequently positive — as is evident, for instance, from the electrocardiograms reported in a previous paper (6) covering 23 cases of anterior wall infarction. Consequently, CF is more likely to present an inversion of T than is CR, and if both CF and CR show inversion of T, the T wave will be more negative in CF.

On the basis of the RS-T and T changes, then, it seems safe to conclude that even though CR may be superior to CF in acute cases with elevation of RS- T_2 and subsequent negative T_2 , CF is preferable because it is superior to CR in most of the cases which give no specific changes on derivation from the extremities, that is, in the very cases where precordial leads are required.

In precordial leads, however, the QRS changes are even more important than the RS-T and T changes because they keep constant and thus are highly contributory to meet the purpose of precordial leads: to make the diagnosis of infarction at a point of time when it cannot be made by derivation from the extremities. It is of the greatest interest, therefore, to see how the QRS changes behave in CR and CF. But here we meet with the difficulty that the QRS changes are not so easy to appreciate as the RS-T and T changes because in our considerations we have to reckon with simultaneous deflections, and it is not safe without a more thorough investigation to presuppose that Q, R and S in Lead II and in the precordial leads are simultaneous. Still, it is practicable to establish certain facts concerning this point.

According to most previous authors, the typical QRS changes in precordial leads in cases of anterior wall infarction consist in absence or diminution of R. According to our own investigations (6, 7), complete absence of the R wave in anterior wall infarction is found only in some of the cases and often only in the medial precordial leads. In many cases the R wave is preserved completely or partially, but then it is preceded by a relatively large Q wave.

So the QRS change most characteristic of anterior wall infarction is the presence of an enormously large, initially negative, deflection. This abnormality is more likely to appear in CF than in CR, as in anterior wall infarction the initial part of the QRS complex in Lead II most often is positive.

This fact, which has not been presented previously, speaks very strongly in favor of the employment of CF for routine derivation, as the diagnosis of chronic anterior wall infarction often can be made only on the QRS changes in precordial leads.

In *posterior wall infarction* the electrocardiograms taken with derivations from the extremities are most often very typical, and precordial leads are of no direct diagnostic value. But the latter ought to be employed anyhow in every case, because they may serve to confirm that the lesion involves exclusively a posterior wall infarct (a combination of posterior wall + anterior wall infarction is very frequent; in an autopsy material comprising 51 cases from the Medical Dep. B of the Rigshospital this combination was encountered in 20). The precordial lead changes typical of entirely posterior wall infarction consist in depression of RS-T in the acute stage, positive T wave and preserved initial R wave, that is, changes contrary to those in anterior wall infarction. The features typical of posterior wall infarction are presented more strikingly by CF than by CR, as Lead II shows elevation of RS-T and negative T besides frequently a large wide Q wave. CR is more likely than CF to show inversion of the T wave (T_2 negative), but this is no advantage, as in these cases the diagnosis as a rule is quite established by the extremity leads, and an inversion of T could only be confusing, as it would be suggestive of anterior wall or lateral infarction. For the same reason, it is no advantage that CR is more likely than CF to show a diminution of the R wave (with a large wide Q_2).

All told, from theoretical considerations CF must be said to be more suitable than CR for the diagnosis of cardiac infarction. That CF is more suitable than CL is easy to demonstrate by employment of the relation $CL = CF + III$ in quite a similar manner as above. How great the difference between CF and CR is in practice may be shown only by a clinical material (the collection of such a material has been commenced). As suggested also by Geiger's (3) findings, it is rather likely that CF and CR

in a good many cases will prove equally valuable because the changes in *both* CR and CF are so pronounced that the influence of the peripheral electrode becomes unessential.

That the above considerations are not only of theoretical significance, however, is shown by our experiences so far from clinical cases of cardiac infarction, among which the following is particularly instructive.

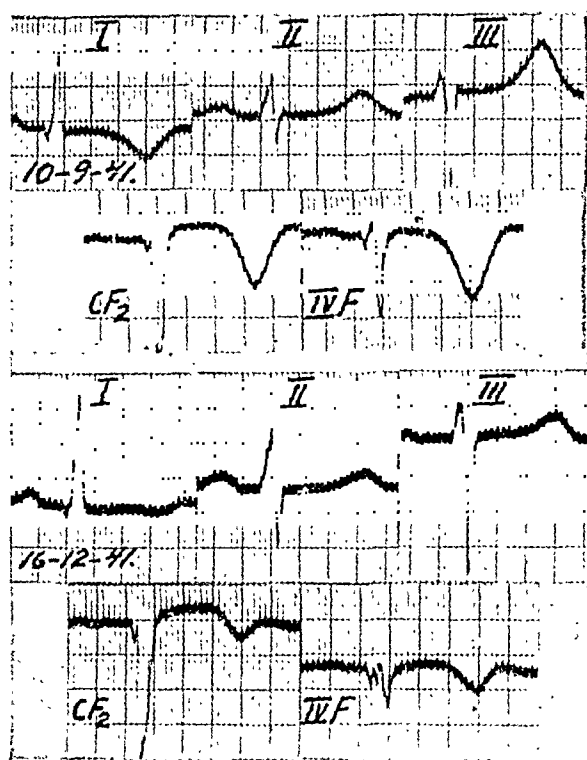


Fig. 3. Two electrocardiograms, taken respectively about 1 and 4 months after an attack of acute coronary occlusion. The changes are typical of anterior wall infarction.

This patient is a man, 71 years old, who was admitted to Medical Dep. B of the Rigshospital on 11/8/41 (Record No. 716/41) immediately after an attack of acute coronary occlusion. Electrocardiograms taken on admission showed a suggestion of elevation of RS-T₁ and depression of RS-T₂ and RS-T₃. The following electrocardiograms showed development of very typical RS-T and T changes in extremity and precordial leads characteristic of anterior wall infarction. These changes reached the maximum about 10/9 (see Fig. 3), whereafter they commenced

tu subside. Till 19/3/42 a total of 40 electrocardiograms were taken; of precordial leads, only CR₂ and IVR were employed in 15, only CF₂ and IVF in 7, while in 18 electrocardiograms CR₂ was employed simultaneously with CF₂ and IVR simultaneously with IVF, besides several other precordial leads. All the electrocardiograms taken with CF₂ and IVF showed very typical QRS changes, whereas none of the electrocardiograms taken with CR₂ and IVR showed any QRS changes. Fig. 3 shows two

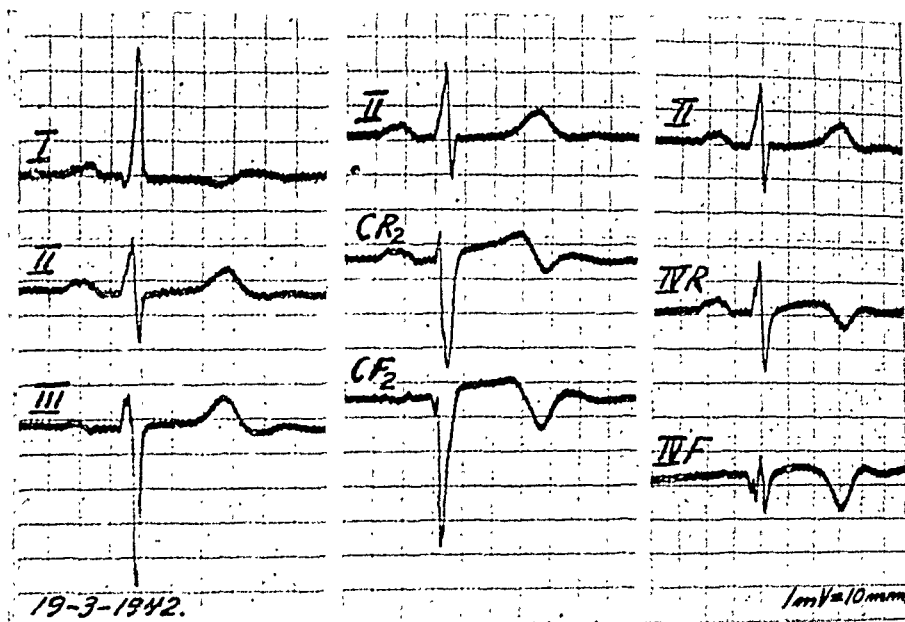


Fig. 4. Electrocardiogram from the same case as Fig. 3, taken about 7 months after the attack. Pronounced QRS changes typical of anterior wall infarction in CF₂ and IVF; no QRS changes in CR₂ and IVR (taken simultaneously with CF₂ and IVF, respectively).

electrocardiograms picked out of this series; they show very clearly that the lesion was an anterior wall infarction. Fig. 4 shows an electrocardiogram taken about 7 months after the attack. CF₂ and IVF show very typical QRS changes, whereas no QRS changes are seen in CR₂ and IVR, which were taken simultaneously with CF₂ and IVF, respectively.

Concerning the arguments advanced in favor of the employment of CR, the following remarks are to be made:

1) Undoubtedly it is an advantage that CR in normal subjects is more constant than CF. But this greater stability in normal

extremity electrocardiograms is obtained only at the expence of the sensitiveness of the derivation, as myocardial affections which are not sufficiently advanced to affect the extremity electrocardiograms are more likely to be registered in CF than in CR. On the other hand, this greater sensitiveness involves the risk that T occasionally may be inverted even when the heart is normal. This source of error is relatively harmless, however, as the inversion of T with a normal heart appears only in comparatively rare cases, in particularly in young persons with a pendulous heart, and only in the parasternal leads.

2) That the deflections in CR are greater than those in CF holds good probably most often for normal subjects, in whom the main deflections in Lead II are positive. But, as is evident from the preceding this rule is by no means of universal validity.

3) The difficulty emphasized by Deeds & Barnes (2) in keeping the isoelectrical level constant in taking electrocardiograms with CF is something we have never experienced.

4) Whether we have to change one or two connections of leads is quite immaterial if only CF offers the least diagnostic advantage over CR.

From the above we have arrived at the conclusion that theoretical considerations together with the clinical experiences so far indicate that in the routine employment of precordial leads it is more expedient to place the peripheral electrode on the left leg.

Summary.

The question about the most serviceable location of the peripheral (indifferent) electrode in precordial leads has not been solved yet.

Wolferth & Wood have shown that none of Leads CR, CL and CF is superior to the other two by giving greater or smaller deflections in all cases. Some deflections are more striking in CR, some in CL and others in CF, all depending on the situation of the electrical axis for the part of the electrocardiogram concerned.

It is pointed out that, from theoretical considerations, CF is more suitable than CR for the diagnosis of cardiac infarction,

and a case of anterior wall infarction is demonstrated in which typical QRS changes were found in CF₂ and IVF, while QRS changes were absent in CR₂ and IVR.

As precordial leads are of the greatest value to the diagnosis of cardiac infarction and, in comparison hereto, only of slight practical value in other fields, it will be most rational for routine derivation to employ the precordial lead that is most serviceable for the diagnosis of cardiac infarction. The conclusion is drawn that theoretical considerations together with the clinical experience gathered so far indicate that in the routine employment of precordial leads it is most expedient to place the peripheral electrode on the left leg.

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On establishing the presence of tuberculosis bacilli by means of the fluorescence microscope.

By

ANNA ANDERSSON.

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In close association with the advances which have been made within the field of virus research during recent years, researches dealing with the tuberculosis bacillus have become increasingly intensive, both in the matter of elucidating its morphology and of creating more effective methods for proving its presence.

Since Ziehl-Nielsen (referred to below as Z—N.) published his method of staining tuberculosis bacilli in 1885, which has probably been that most employed up to the present time, a number of different modifications of it, as well as entirely new methods, have been worked out with the object of improving on it. The chief drawback of Z—N. staining has been considered to be that a sufficiently sharp contrast effect was not obtained between the red bacilli and the blue background, and that the counter staining with methylene blue is apt to become too strong, so that the tuberculosis bacilli are covered by it and are liable to be overlooked, especially in thick preparations. In working on the improvement of the Z—N. staining other stains have been selected for contrast stains, or other staining fluids (Konrich, Jötten-Haarman, Spengler), to eliminate this objection. In comparative investigations, sometimes one sometimes another of these modifications has been considered superior to Z-N., but this has not yet led to the abandonment of Z-N. staining, and it still remains the generally accepted method. In more recent years, however, two staining methods have been worked out, which, judging from the favourable post-examinations

which have already been published, will probably imply an improvement, namely fluorescence microscopy according to Hagemann and night-blue staining according to Hallberg.

Fluorescence microscopy has been known since 1911, when H. Lehmann constructed the first fluorescence microscope. At first it was employed within bacteriology to establish the primary fluorescence of certain bacteria and species of fungi. In 1929 Bommer (Berlin) introduced the method within the field of zoology, and since 1923 Haitinger and Linsbauer (Vienna) have worked it up further and extended its employment to include biology and histology as well. However, it was Hagemann who, in 1937, first introduced fluorescence microscopy into the field of virus research and bacteriology, to establish the presence of bacilli, especially tuberculosis bacilli.

The fact that fluorescence microscopy (designated fl. m. below) has proved superior to Z-N has emerged from a number of comparative investigations, although these have not given uniform results. In one respect, however, there is complete agreement: the method saves a great deal of time, the bacilli appearing larger than with the use of ordinary stainings and being seen clearly, even with lower magnification, e. g. 600 times, which renders the immersion lens unnecessary. In this way the field of vision becomes larger and a better survey of the preparation is obtained. But these are not the only advantages. It has been proved in many places that tuberculosis bacilli (tbb.) are found in a larger number of cases and with greater certainty with fl. m. than with Z-N. and other staining methods; Hagemann, for instance, found the method nearly 100 % safer. The following authors have also obtained better results with fl. m.: Hermann, Clauberg, Küster, Luz and Meding, Jung, Backman, Gärtner, Didion, Rega-Nour, Tenkert, Kristoferson, Larsen, Thomassen, Schneider, and others. Particulars as to the so-called »greater effect» i. e. greater number of positive tests with fl. m. than with Z-N. vary, however, from 6 to 71 %. Gärtner indicated 20 % as a mean figure. The lack of uniformity will be partly due to the difficulty of attaining complete objectivity in investigations of this type. Dabelstein and Grothnes are almost alone in considering Z-N. equally good as fl. m., and the superiority of the latter will probably be almost undisputed nowadays. The reason for this has not yet been elucidated, however,

although a number of different explanations have been advanced. Hagemann and Hermann consider that more bacilli are stained with the fl. m. stains and base their statements on their bacteria counts. Didion also made bacteria counts but did not arrive at the same result. In his comparative investigations Gerhard Larsen studied a preparation for a certain time and determined the area of the surface of the preparation examined. According to his opinion the »greater effect» with fl. m. is due to the fact that with this method, owing to the lesser degree of magnification, considerably larger surfaces are examined in the same time than in the case of the other staining methods. Bachmann, Clauberg, Didion, etc. hold the same opinion, and further they emphasize the circumstance that, owing to their emitted light, the bacilli are easier to discover, and that they shine through particles of mucus, etc.

We then come to the method worked out by Hallberg in 1939, which has also been considered an improvement on Z-N. With this method a different and sharper contrast effect is obtained than with Z-N. The carbolfuchsin is replaced by »night-blue» (Grübler) in a concentration of $\frac{1}{4}$ — $\frac{1}{2}$ % in 2.5 % carbolic acid solution, and the after-staining is effected with diluted carbolfuchsin or neutral red. The bacilli appear dark-blue on a light-red ground and appear larger than with Z-N. In post-examinations by Kristensson and Gerhard Larsen better results have been obtained with Hallberg staining (H) than with Z-N.

The author's investigations.

At Fur Sanatorium fl. m. has been employed since 1940 in the daily routine work, the great advantages of the method as regards time-saving and simplicity of working being completely confirmed. Staining according to H. has also been tested, and although many comparative investigations have already been made, we have found of interest an investigation of this kind, in which we directed our attention particularly to the question whether any of these methods give such certain results that they might conceivably replace the culture of tbb. As we did not find that the comparative methods employed earlier fully satisfy the claims for scientific objectivity that one is entitled to impose, we have endeavoured, by means of photographing one and the same field of vision in a microscopic

preparation stained according to all three methods in succession, to investigate objectively whether the claimed superiority of fl. m. and H. staining is due to a larger number of bacilli being stained, or whether it is due to other factors.

A total of 1503 sputa were examined; and the mode of procedure was as follows: the sputum was divided as equally as possible between two object glasses, one being stained with auramine according to Hagemann's directions and the other first according to Z-N. and subsequently according to Hallberg, which can be done without any inconvenience. Examination of the preparations stained with auramine and Z-N. was made by different investigators independently of each other, and of the preparation stained according to H. by the same investigators as for fl. m., but without the previous results being disclosed. The preparations were examined for about 5 mins. before they were declared to be negative. In all the cases where bacilli could not be established according to Z-N., cultures were made on Löwenstein's medium. In about the first 100 cases 3 tubes were used for every test. As, however, in all the positive cases growth was practically always obtained in all three tubes, we began to use only one tube, for reasons of economy. The tubes were examined frequently and were read off after 4 and 8 weeks. Growth could usually be observed after 4 weeks, and only in a few cases did it come later. In all the cases characterized as positive, tbb. was checked with the microscope, even if the colonies were fully typical of tuberculosis.

Results:

The examinations were made in 2 different series, the first comprising 149 cases where a comparison was made between fl. m. and Z-N.; the second series comprised 1354 cases, a comparison being made between fl. m., H. and Z-N.

Series I.

A comparison between fl. m. and Z-N. (149 cases).

Table 1 a.

	pos.	neg.	pos. as % of the total no.	pos. as % calculat- ed on the no. Z-N. pos.
Fluorescence mic.	97	52	65	21
Ziehl-Nielsen	80	69	53	—

Table 1 b.

Culture of the 69 Z—N. negative cases.

	pos.	neg.	no. pos. in %
Culture	28	41	40
Fluorescence mic.	17	52	25
Ziehl-Nielsen	0	69	—

From table 1 a it emerges that 97 preparations were positive with fl. m. and 80 with Z-N., which gives a superiority for fl. m. of 21 % (calculated on the Z-N. positive cases). In all the Z-N. negative cases cultures were made, and as is shown by table 1 b, 28 then proved to be positive. Among the 28 there were also 17 which were positive with fl. m. No case was pos. with fl. m. and negative in culture, 11 cases being positive only in culture.

Series II.

A comparison between fl. m., H. and Z-N. (1354 cases).

Table 2 a.

	pos.	neg.	no. pos. as % of the total	no. pos. as % calcul- ated on the Z-N. pos.
Fluorescence mic.	846	508	61	21
Hallberg	745	609	55	6
Ziehl-Nielsen	703	651	51	—

Table 2 b.

Culture of the 651 Z—N. negative cases.

	pos.	neg.	no. pos. as %
Culture	241	410	36
Fluorescence mic.	143	508	22
Hallberg	42	609	6.4
Ziehl-Nielsen	0	651	—

As is shown in table 2 a, 846 cases were pos. according to fl. m., 745 according to H. and 703 according to Z-N. Calculated as a percentage of the Z-N. pos. cases, this gives a superiority for fl. m. of 21 % as against Z-N., and on the same basis of calculation of 13 % as against H. This in its turn, and on the same basis of calculation, is 6 % better than Z-N. Thus 651 cases were negative with Z-N. In table 3 is shown how many of them were positive on culture alone or with either of the other two staining methods, and their relation to each other.

Table 3.

Positive.		Positive.	
Culture & fl. m.	94	Fl. m. (only)	40
Culture & H.	19	H. (only)	17
Culture & fl.m. & H.	6		
Culture (only)	122		
<hr/>		<hr/>	
Total	241	Total	57

Thus 298 cases were positive with some one of the other methods among the 651 Z-N. neg. cases. In the whole series (1354 cases) 353 were negative by all methods.

Culture has thus proved to be superior to the staining methods in that in 122 cases the presence of bacilli could be proved only by culture. In 57 cases, however, cultures gave negative results in cases where some one of the staining methods had been pos. (fl. m. 40 and H. 17 cases). The circumstance that tbb. were established in the same patient on another occasion, either by cultures or guinea pig tests, also supports the fact that, even in these cases, it was a matter of tbb. and not other acid-fast staves.

Thus, fl. m. has proved to be superior to both Z-N. and H. but there can be no question of its supplanting cultures of tbb. As all the specimens were examined very carefully, it is hard likely that any more pos. specimens would be obtained by a post-examination.

Series III.

Photographic studies. (17 cases)

In taking photographs the mode of procedure was as follows: the preparation was first stained according to one method. A certain field of vision was marked out by cutting a ring on the object-slide with a diamond. The ring was placed centrally in the objective, a drawing of the ringed-in field of vision made, and the position of the bacilli in the field of vision drawn. After that we took the photograph, then restained the preparation according to another method, and with the guidance of the ring and the drawing adjusted it in exactly the same field of vision, took a fresh photograph, and then stained it again according to the third method and photographed it again. In this way it was possible to calculate the number of bacilli on the different photographs of the same field of

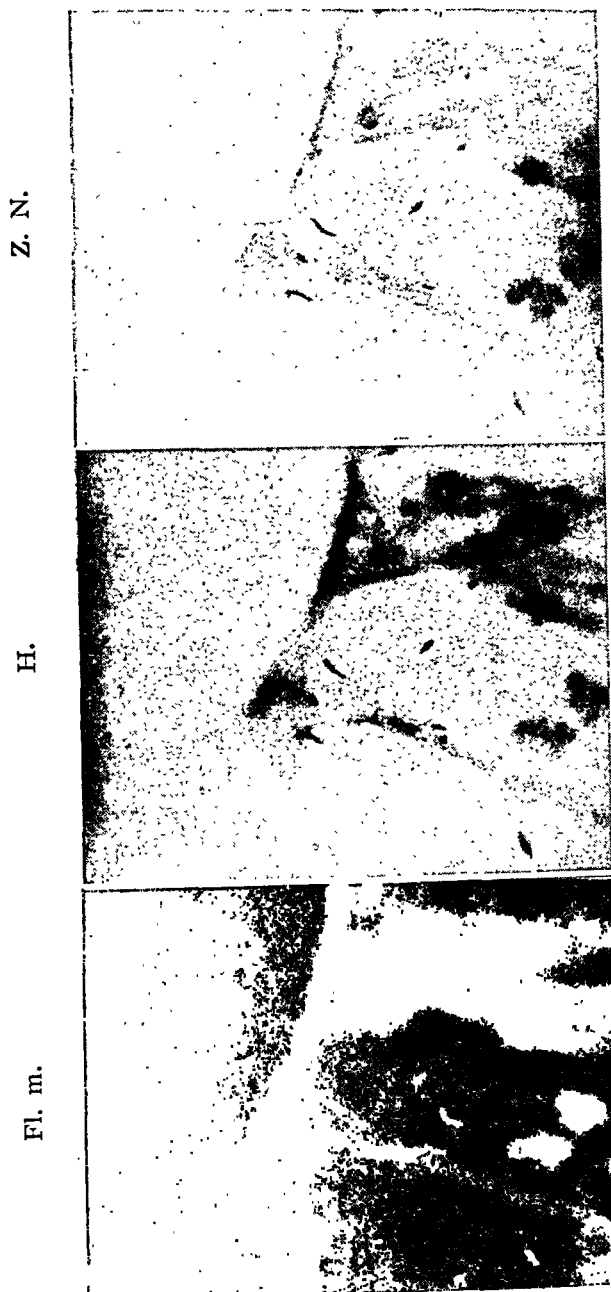
vision in a certain preparation stained according to all three methods, and a completely objective basis for comparison was thus obtained.

To exclude the possibility of a number of bacilli being damaged and losing their stainability during the different staining procedures, we arranged different series, in which sometimes one and sometimes another of the stainings was done first, altogether more than 200 preparations being thus treated. No difference in stainability in this respect was ever observed, however.

It appears from the photographs that the same number of bacilli were stained with Z-N. and H. but that more were stained with auramine. On the other hand, the bacilli appear larger and more clearly with H. staining, particularly in thick preparations. In a number of photographs it looks as though more bacilli were stained according to H., but on closer scrutiny the same bacilli can also be discerned with Z-N., although they are partly covered and do not appear so clearly. As is shown by the illustrations below, bacilli are seen in the field of vision with auramine staining where none can be found on the corresponding spot with either Z-N. or H. That this circumstance can be due to bad staining is out of the question, since bacilli appear clearly in other places in the same field of vision.

Summary and conclusion.

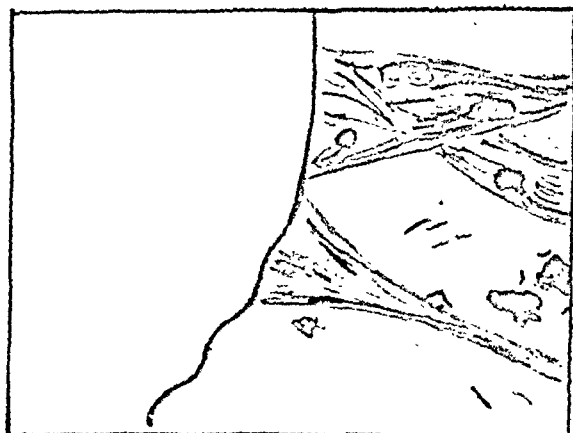
A comparative examination was made between 3 methods of proving tuberculosis bacilli, namely fluorescence microscopy and staining according to Ziehl-Nielsen and Hallberg. In all the cases which were negative with Z-N. cultures were also made. An examination of 1503 sputa in 2 series showed that fl. m. is superior to both the other methods of staining, and that staining according to H. gives better results than according to Z-N. With regard to the cause of this, the photographic studies justify the conclusion that the superiority of fl. m. does not lie only in the saving of time, etc. but also in the fact that more bacilli are stained by this method than by the 2 others, which will be the most important consideration. In the case of Hallberg-staining we did not find that more bacilli were stained, but the reason why better results are obtained with this method than with Ziehl-Nielsen will probably be that the



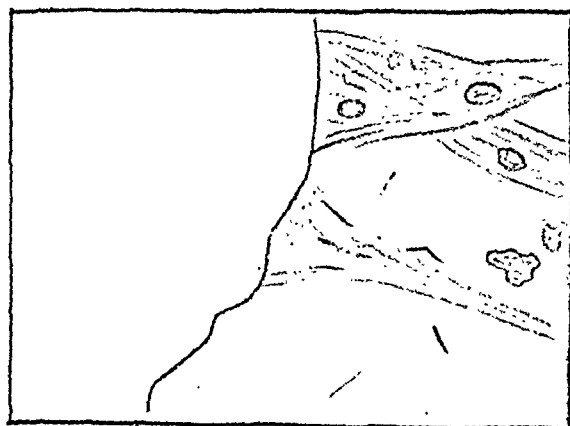
Photograph I.

In this field of vision are found 10 tubercle bac. with fl.m., 7 with H. and Z—N. The bacilli most strongly marked on the drawing could not be found on either the H. or the Z—N. photographs. Several stainings were made in succession, and always the same bacilli were stained.

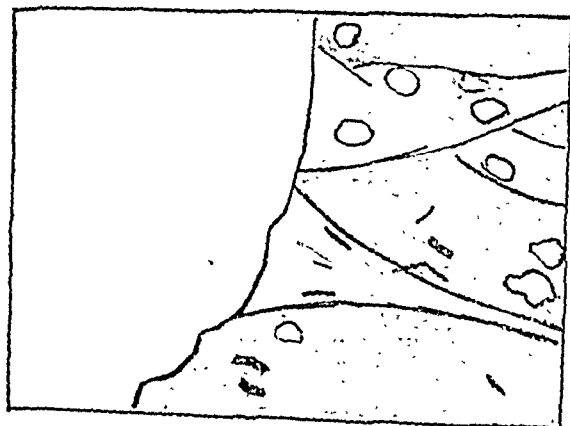
Acta Medica Scandinavica, Vol. CXV, fasc. V.
Andersson: On establishing the presence etc.



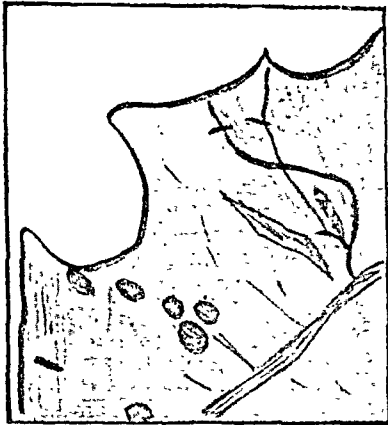
7 tbb.



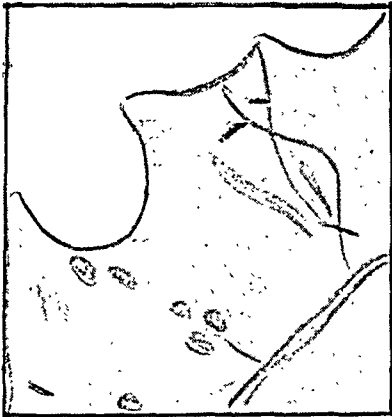
7 tbb.



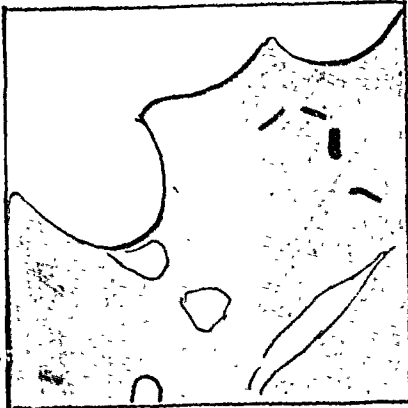
10 tbb.



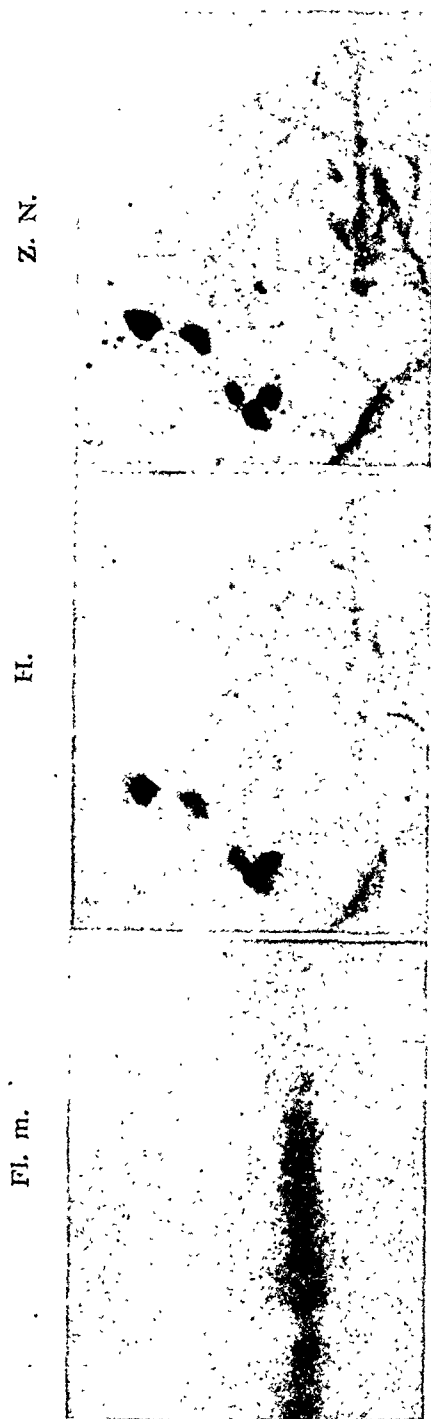
4 tbb.



4 tbb.



5 tbb.



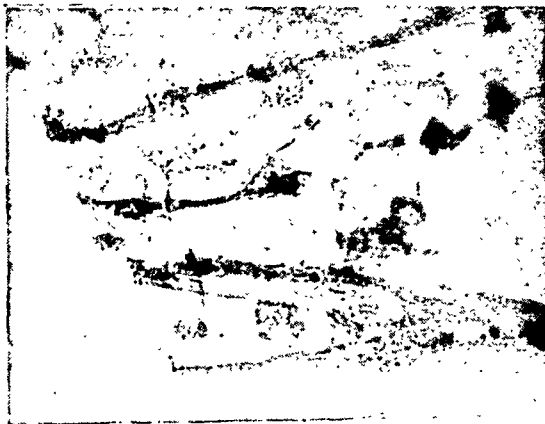
Photograph II.

In this there are 5 tbb. according to fl.m. and 4 with H. and Z—N.

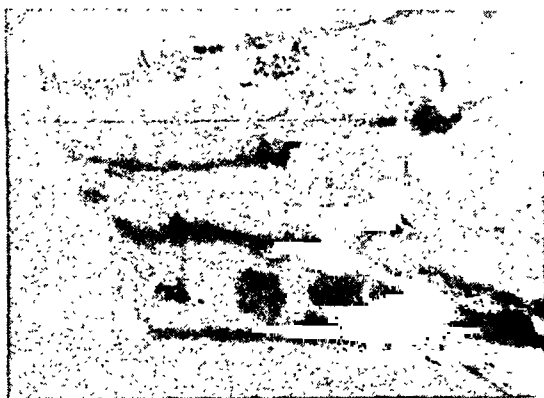
Fl. m.



H.



Z. N;



Photograph III.

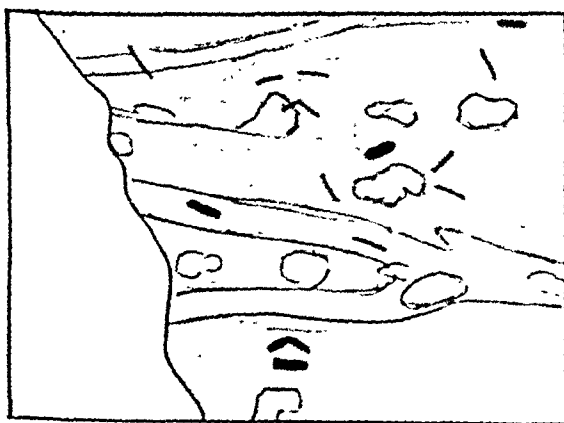
In this field of vision 15 tbb. are seen on the fl. m. photograph, 9 on the H. and 10 on the Z—N. On the Z—N photograph there is 1 bacillus which cannot be found on the corresponding spot on the others. On the other hand, on the fl. m. photograph 5 bacilli (strongly marked on the drawing) are seen, which cannot be detected on either the H. or the Z—N. photographs.



10 tbb.



9 tbb.



15 tbb.

bacilli are larger and easier to discover, owing to better contrast conditions. Further, we found that the most certain results in establishing tuberculosis bacilli are obtained by means of cultures, which cannot possibly be replaced by fl. m.

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Die Senkungsreaktion bei perniziöser Anämie.

Von

RAGNAR BERLIN.

(Bei der Redaktion am 23. Juli 1943 eingegangen).

Während der letzten Jahre ist ein gesteigertes Interesse für die S. R. bei verschiedenen Anämieformen entstanden, und in diesem Zusammenhang hat auch die häufig extrem erhöhte S. R. bei perniziöser Anämie die Aufmerksamkeit auf sich gezogen.

Es ist allerdings erstaunlich festzustellen, wie wenig man eigentlich über die Ursachen für die erhöhte S. R. bei anämia perniciosa weiss, abgesehen von der Erhöhung, die durch den herabgesetzten Gehalt an roten Blutkörperchen herbeigeführt wird. Mehrere Verfasser haben sich zwar ziemlich eingehend mit den hierhergehörenden Problemen beschäftigt, ohne jedoch weiter als zu Vermutungen zu kommen, und die meisten Verfasser haben darauf hingewiesen, dass keiner der bisher als senkungserhöhend bekannten Faktoren das Phänomen völlig erklären kann. (Bendien, Neuberg, Snapper; Westergren, Theorell, Widström; Reichel u. a.) Diese Verfasser nehmen an, dass ein oder einige unbekannte Umstände vorhanden sein müssen, die gerade bei perniziöser Anämie die Aggregationstendenz der roten Blutkörperchen beeinflussen.

Bekanntlich ist eine erhöhte S. R. im allgemeinen durch einen erhöhten Gehalt an Fibrinogen oder Globulin oder beide im Plasma bedingt. (Fåhræus u. a.) Ausserdem wirkt eine Verringerung der Blutkörperchenkonzentration erhöhend auf die Senkungsreaktion; wenn man Blut in vitro mit Eigenplasma verdünnt,

kann diese Verhältnis leicht demonstriert werden. (Fähræus; Westergren; Bendien, Neuberg und Snapper u. a.)

Was den verringerten Gehalt an roten Blutkörperchen betrifft, der bei Anämien vorhanden ist, zeigt bereits die einfache klinische Beobachtung, dass dieser nicht allein die Ursache für die hohe S.R. der perniziösen Anämie sein kann. Wenn man nämlich eine schwere posthämorrhagische Anämie oder eine essentiell hypokrome Anämie mit einem Perniciosafall mit gleicher Blutkörperchenzahl vergleicht, so zeigt der letztere Fall oft eine bedeutend höhere S. R. (Bendien, Neuberg und Snapper, Reichel, u. a.) Diese niedrigere S. R. bei z. B. den posthämorrhagischen Anämien liesse sich dadurch erklären, dass eine erhöhte Menge von Reticulocyten mit verringerter Aggregationstendenz in das periphere Blut ausgeschwemmt ist und senkungshemmend wirkt. Dass mit diesen Verhältnissen aber zumindest nicht immer zu rechnen ist, zeigt ein Fall akuter Arterienblutung vom Magensack, den zu beobachten ich vor einiger Zeit Gelegenheit hatte. Der Mann hatte in der kurzen Zeit von reichlich 24 Stunden soviel Blut verloren, dass er trotz wiederholter Bluttransfusionen so niedrige Blutwerte wie Hb 17 und 0.92 Millionen rote Blutkörperchen aufwies. Die Reticulocytenzahl war beinahe normal (15 promille). Er hatte trotzdem eine S. R., die nicht höher als 27 mm war. Ein Fall von perniziöser Anämie mit derart niedrigen Blutwerten zeigt, wie bekannt, praktisch immer bedeutend höhere Senkungswerte.

Um weiterhin die Frage zu beleuchten, wie gross die Einwirkung ist, welche die Anämie auf die Senkungsverhältnisse hat, habe ich in fünf normalen Fällen Blut mit Eigenplasma verdünnt und nach einer Stunde die S. R. bestimmt. Fig. 1 zeigt das Resultat, und das Wesentlichste, welches man aus der Kurve ablesen kann, ist, dass die S. R. innerhalb der Grenzen für die klinisch vorkommenden Werte kaum über 60 mm geht. Sehr häufig treffen wir jedoch in der Praxis auf Fälle von Perniciosa, die eine S. R. von 100 mm und weit darüber hinaus aufweisen, und dies sogar bei verhältnismässig beibehaltenen Blutwerten.

Unter anderen Erklärungsversuchen hat man auch darauf hingewiesen, dass die roten Blutkörperchen bei pern. Anämie ein höheres spezifisches Gewicht haben sollen und es versteht sich, dass dieser Faktor in extremen Fällen von Bedeutung sein kann. Nasat-haka Ohno zeigte z. B., dass sich die S. R. für rote Blutkörperchen,

in Hayems Lösung aufgeschlämmt, proportional zum Farbindex der Blutkörperchen verhielt, und Oestreich hat direkt gezeigt, dass Blutkörperchen bei perniziöser Anämie ein höheres spezifisches Gewicht hatten als normale Blutkörperchen.

Es zeigt sich weiter, dass die verschiedenen Eiweissfraktionen im Plasma bei Perniciosa in der Regel bei den normalen Werten liegen; oft zeigen Fälle von pern. Anämie sogar subnormale Eiweisswerte. So betont z. B. Kisch, dass niedriger Fibrinogengehalt ein konstanter Befund bei Perniciosa ist, genau so wie bei den meisten anderen schweren Anämien, und Barsky weist auf die allgemeine Reduktion der Plasmaproteine hin, die jedoch meist die Albuminfraktionen treffen sollen. Meulengracht, Iversen und Nakazawa haben Untersuchungen der Eiweissfraktionen bei verschiedenen Anämieformen vorgenommen und abnorm niedrige Werte besonders in den Fällen, die Ödem aufweisen, gefunden. Bendien und Snapper, die sich eingehend mit hierhergehörenden Fragen beschäftigt haben, geben unter ihren 118 Fällen von einem gemischten klinischen Material 2 Fälle von Perniciosa an, wo der Fibrinogen- und Serumglobulingehalt vollkommen normal war. Bendien, Neuberg und Snapper veröffentlichen 2 andere Fälle; in dem einen lag der Fibrinogengehalt dicht oberhalb dem normalen, in dem anderen war er erhöht. Die Serumglobulinwerte waren in beiden Fällen normal. Diese Verfasser weisen darauf hin, dass die Anämie nur zum Teil die hohe S. R. erklären kann, und dass diese jedenfalls höher läge, als die Eiweissanalysen zu vermuten Anlass geben.

Mehrere Forscher, z. B. Bendien, Neuberg und Snapper; Westergren, Theorell und Widström, haben verschiedene empirische Formeln für die Berechnung der S. R. aufgestellt, die mit Rücksicht auf alle oben hervorgehobenen Faktoren entstehen sollte. Es zeigt sich jedoch, dass diese Formeln vielfach nur approximativ für Fälle von perniziöser Anämie gelten. Die letzterwähnten Verfasser heben ihre 2 Perniciösa-fälle hervor, wo der berechnete S. R.-wert wesentlich von dem beobachteten abwich. Auch in Bings und Jessens Zusammenstellung kann man in einem Perniciösa-fall dieselbe mangelnde Übereinstimmung feststellen.

Es ist also, nach der Litteratur zu beurteilen, deutlich, dass keine wirkliche Klarheit in diesen Fragen gewonnen ist, und wenn auch in gewissen Einzelheiten Auffassung gegen Auffassung steht, scheinen doch sämtliche Verfasser darüber einig sein, dass die

bisher bekannten senkungsbefördernden Faktoren nicht ausreichen, um die Ursache für die oft erheblich erhöhte Senkungsreaktion bei perniziöser Anämie zu erklären.

In einer früheren Arbeit (Berlin 1939) habe ich das Problem der erhöhten S. R. der perniziösen Anämie von mehr theoretischen Ausgangspunkten behandelt. Durch einen einfachen Versuch habe ich dort gezeigt, dass ein ganz neuer Faktor bei der Beurteilung der Senkungsgeschwindigkeit bei dieser Krankheit in Betracht gezogen werden muss. Ich habe später den Versuch unter teilweise anderen Bedingungen wiederholt, was aus dem weiter unten angeführten Versuch hervorgeht.

Die NaClgewaschenen Blutkörperchen einer Normalperson von derselben Blutgruppe wie ein Patient mit perniziöser Anämie werden in kleiner und gleicher Menge in zwei Röhrchen mit derselben Menge Zitratplasma versetzt, das eine mit dem der Normalperson, das andere mit dem des Perniciosapatienten. Die S. R. wird nach einer Stunde bestimmt und die Eiweissanalysen werden gleichzeitig mit beiden Plasmaproben ausgeführt.¹ Die Methodik in Übereinstimmung mit den Beschreibungen, die von Theorell und Widström veröffentlicht sind. Das Resultat geht aus Tabelle 1 hervor.

Tabelle 1.

Plasma von	Albumin ‰	Serum-globulin ‰	Fibrinogen ‰	S. R.
Normalperson ...	54.8	22.7	2.8	26
Perniciosafall	44.0	18.3	2.9	46

Wie ersichtlich können sich bei diesem Versuch weder die Eiweissfraktionen, noch die Verdünnung und die verschiedenen Eigenschaften der Blutkörperchen bei dem beobachteten Unterschied in der S. R. geltend machen. Ein etwaiger Unterschied in der Viscosität des Plasmas dürfte von einer so geringen Grössenordnung sein, dass er keine wesentliche Rolle in der Auseinandersetzung spielt. Man wird deshalb gezwungen, das Vorhandensein eines anderen und entscheidenden Faktors anzunehmen, um die Erklä-

¹ Die Eiweissanalysen sind von cand. med. L. Hesselvik beim medizinisch-chemischen Institut in Upsala ausgeführt worden. Ich danke ihm hiermit für die wertvolle Hilfe.

mal mit Äther gewaschen, und dann in einer 1 cm³ phys. Kochsalzlösung gelöst. Mit dieser Lösung als Ausgangspunkt wird eine Konzentrationsreihe 1/2, 1/4, 1/8 u. s. w. mit phys. Kochsalzlösung als Verdünnungsflüssigkeit hergestellt.

Gewöhnliche Leukocytenpipetten werden bis zum Merkstrich 1 mit einer 2.5 % Blutkörperchensuspension von einer Normalperson und danach mit den verschiedenen Lysocithinlösungen bis zum Merkstrich 11 gefüllt. Nach einer sorgfältigen Mischung des Inhaltes werden die Pipetten eine Stunde im Thermostat bei 37 Grad und danach noch eine Stunde im Kühlschrank aufbewahrt. Darauf erfolgt die Zählung von nicht hämolysierenden Zellen in der Bürker-Türckschen Zählkammer. Zum Vergleich dient der Inhalt in einer Pipette, die anstatt einer Lysocithinlösung mit phys. Kochsalzlösung gefüllt worden ist. Der Hämolysengrad wird direkt in % des Vergleichswertes angegeben. 90 % Hämolysen wird als vollständige Hämolysen gerechnet.

Der Einfachheit wegen wird zweckmässigerweise der Lysocithin-gehalt in dem untersuchten Serumprobe als »Lysocithinzahl« angegeben, zum Beispiel die niedrigste Konzentration, die vollständige Hämolysen ergab, ist 1/8. Lysocithinzahl: 8.

Diese Methode kann grob erscheinen, gibt aber doch für den praktischen Gebrauch völlig brauchbare Werte. Eine exakte chemische Methode steht, soviel ich weiss, nicht zur Verfügung.

Eine derartige Bestimmung des Lysocithins ist mit den übrigen Analysen in dem vorher referierten Versuch parallel ausgeführt, und die Ergebnisse beider Versuche sind miteinander verglichen worden. Es zeigte sich hierbei, dass sie eine bedeutende Differenz aufwiesen; die Lysocithinzahl in dem Perniciosaplasma war 8, und im Normalplasma 16. (Siehe Tabelle 2). Es will also scheinen, dass hier ein Faktor vorhanden wäre, der möglicherweise von Bedeutung für das Verständnis dieses offenbaren Unterschiedes in der S. R. der beiden Fälle sein kann.

Tabelle 2.

Plasma von	Albumin ‰	Serumglo- bulin ‰	Fibrinogen ‰	Lysocit- hinzahl	S. R.
Normalperson	54.8	22.7	2.8	16	26
Perniciosafall . . .	44.0	18.3	2.9	8	46

Um mehr Klarheit darüber zu gewinnen, inwieweit dies wirklich der Fall ist, habe ich später gleichzeitige Eiweissanalysen und Lysocithinbestimmungen ausgeführt und die S. R. bei zehn verschiedenen Fällen pernicioser Anämie gemessen. Sämtliche Fälle sind sichere Perniciosafälle mit typischem Sternalpunktat gewesen, und alle haben mit hochgradiger Remission auf spezifische Behandlung reagiert (10 cm³ Campolon i. m. an aufeinander folgenden 4 Tagen.)

Zwei dieser Fälle sind nur im Zusammenhang mit der Aufnahme ins Krankenhaus untersucht worden, während die 8 übrigen auch nach der Remission untersucht worden sind. In den Fällen, die auch nach der Behandlung verfolgt wurden, habe ich — ehe die S. R. bestimmt wurde — die Blutkörperchenzahl/mm³ auf ung. die gleiche Zahl wie vor der Behandlung durch Verdünnung der Blutprobe mit Eigenplasma reduziert. Das Ergebnis dieser Untersuchungen geht aus Tabelle 3 hervor.

Um den Unterschied in der S. R. zwischen den untersuchten Perniciosafällen und den gedachten Fällen, in denen die S. R. an

Tabelle 3.

Nr.	Datum	Hb.	R.bltr.	Glob. ‰	Fibr. ‰	Alb. ‰	Lysocithin.	S. R.	Ber. S. R.	Bemerkungen
1.	31. X. 39.	57	1.81	24.8	1.6	12.1	16	28	0	
	15. XII. 39.	79	3.60	28.0	1.6	36.0	16	21	0	
2.	16. XII. 39.	26	0.99	17.7	1.2	28.4	2	151	0	
	1. II. 40.	57	3.18	36.1	1.9	37.5	16	20	32	
3.	25. I. 40.	43	1.42	12.1	0.8	16.9	16	13	0	
	29. II. 40.	63	2.79	39.4	2.6	46.4	16	57	37	Akut. Infekt.
4.	3. II. 40.	57	2.52	29.9	3.0	38.7	8	61	25	
	4. III. 40.	94	4.64	28.7	2.1	43.3	32	8	1	
5.	5. II. 40.	32	1.14	13.1	2.8	36.2	16	25	0	
	20. III. 40.	74	3.90	21.9	2.6	54.8	16	37	0	
6.	9. II. 40.	58	1.98	27.2	2.0	44.4	32	2	0	
	5. IV. 40.	85	3.27	24.7	3.2	57.5	—	121	4	Akut. Infekt.
7.	24. II. 40.	53	1.68	23.5	4.9	54.3	8	80	55	Akut. Infekt.
	20. III. 40.	90	3.81	24.0	2.8	51.9	16	18	0	
8.	5. IV. 40.	53	1.90	26.9	2.8	42.2	8	26	9	
	28. III. 40.	84	3.90	25.9	4.0	60.6	—	38	18	
9.	19. III. 40.	42	1.90	35.9	1.9	36.0	4	124	38	
10.	17. III. 40.	32	1.30	21.9	0.7	31.2	8	48	0	

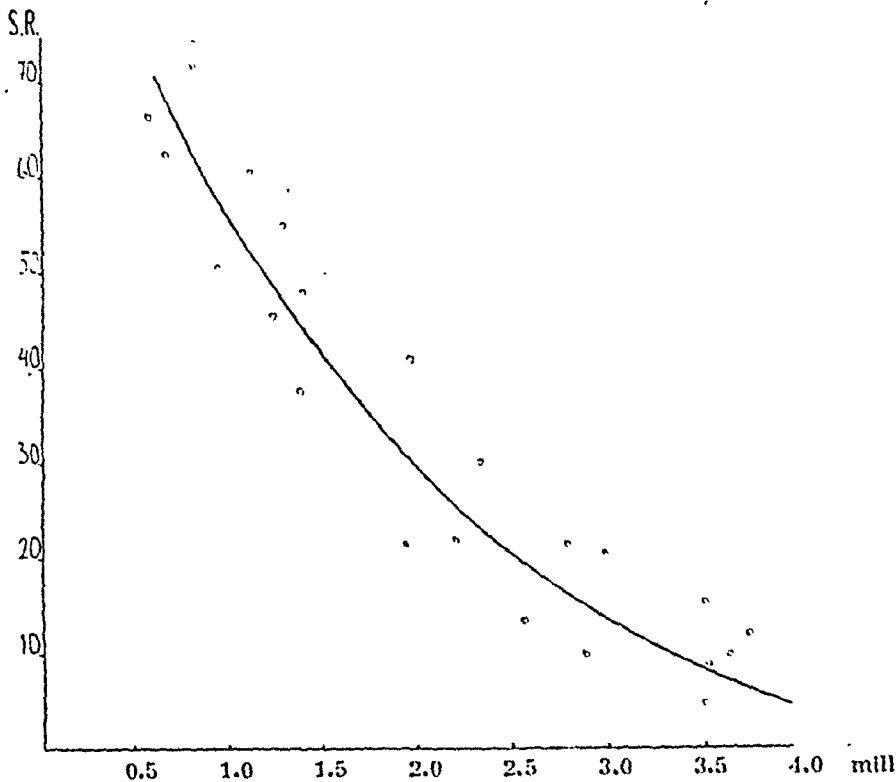


Fig. 1.

Hand der festgestellten Eiweisswerte, der Blutkörperchenzahl, u. s. w. berechnet worden war, deutlicher zu veranschaulichen, habe ich die Formel benutzt, die von Bendien, Neuberg und Snapper aufgestellt worden ist. Es zeigt sich aber, dass diese Formel nicht geeignet ist, dann benutzt zu werden, wenn es sich um Plasma mit so niedrigen Eiweisswerten handelt, wie sie hier in mehreren Fällen vorhanden waren. (Fall 1, 2, 3, 10) und man erhält hierbei auch nicht die geringste Übereinstimmung zwischen dem berechneten und dem wirklichen Wert der S. R. Die Formel ist jedoch benutzt worden, ohne dass Hämatokrituntersuchungen ausgeführt worden waren, aber das Blutkörperchenvolumen ist an der Hand der Blutkörperchenzahl annähernd errechnet worden.

Bei einer Prüfung der Tabelle ist es nämlich auffallend, dass die Eiweisswerte in 4 der unbehandelten Fälle ungewöhnlich niedrig sind; in 5 Fällen liegen sie völlig innerhalb der Normalgrenzen und nur in einem Fall (Fall 7) ist der Fibrinogenwert deutlich erhöht. Dieser Fall hatte jedoch bei der Einlieferung in die Abteilung ausser seiner Perniciosa auch eine akute Luftröhreninfektion.

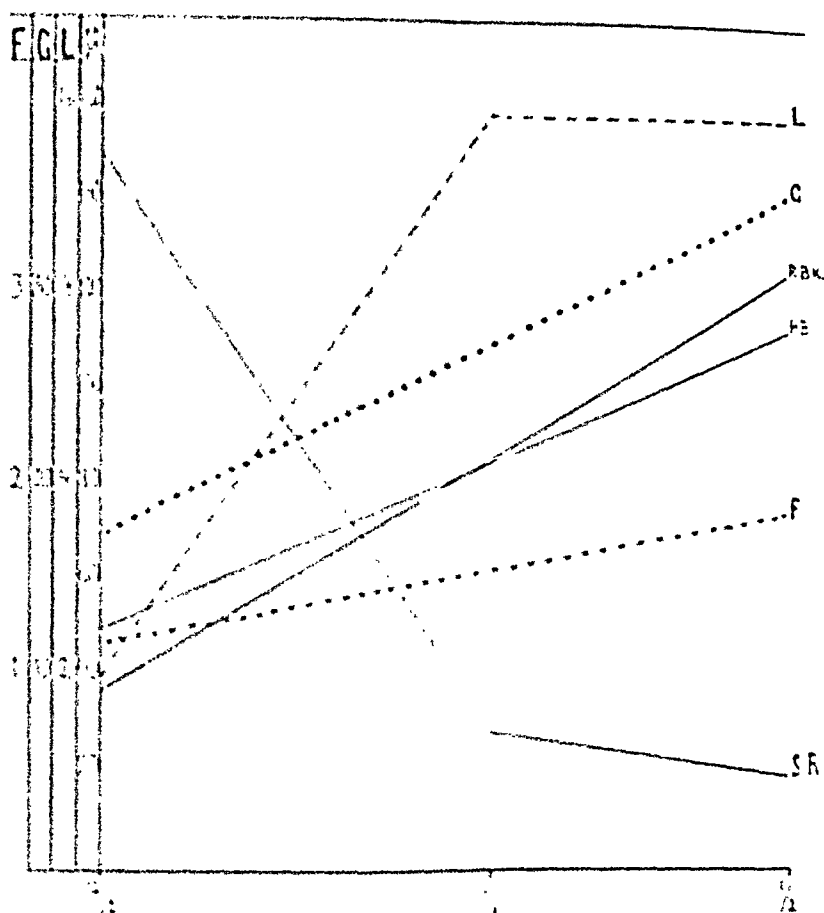


Fig. 2.

— S.R. mm, --- Lysocithinzahl, +++ Fibrinogen $\%$, Globulin $\%$,
 Hb d. $1\frac{1}{2}$ = 26, R.B.K. d. $1\frac{1}{2}$ = 0.97 mill.
 Hb d. $1\frac{1}{2}$ = 55, R.B.K. d. $1\frac{1}{2}$ = 3.17 mill.

Weiter ist es von Interesse zu beobachten, dass die S. R. auch bei diesem nicht sehr umfangreichen Material nicht in allen unbehandelten Fällen stark erhöhte Werte zeigt, was nach Reichel ein ständig vorkommendes Symptom bei perniziöser Anämie sein sollte, und das nach Klar in den allermeisten Fällen vorhanden sein sollte. Die Zusammenstellung zeigt sogar einen Fall mit dem ungewöhnlich niedrigen Werte von 2 mm/1 Stunde. Dieser Fall hatte auch einen Lysocithinwert, der doppelt so hoch war als die als normal angegebene Lysocithinzahl von 16.

Während der Behandlung haben in drei der Fälle die S. R.-Werte deutlich abgenommen, und die Tabelle zeigt auch, wie die Lyso-

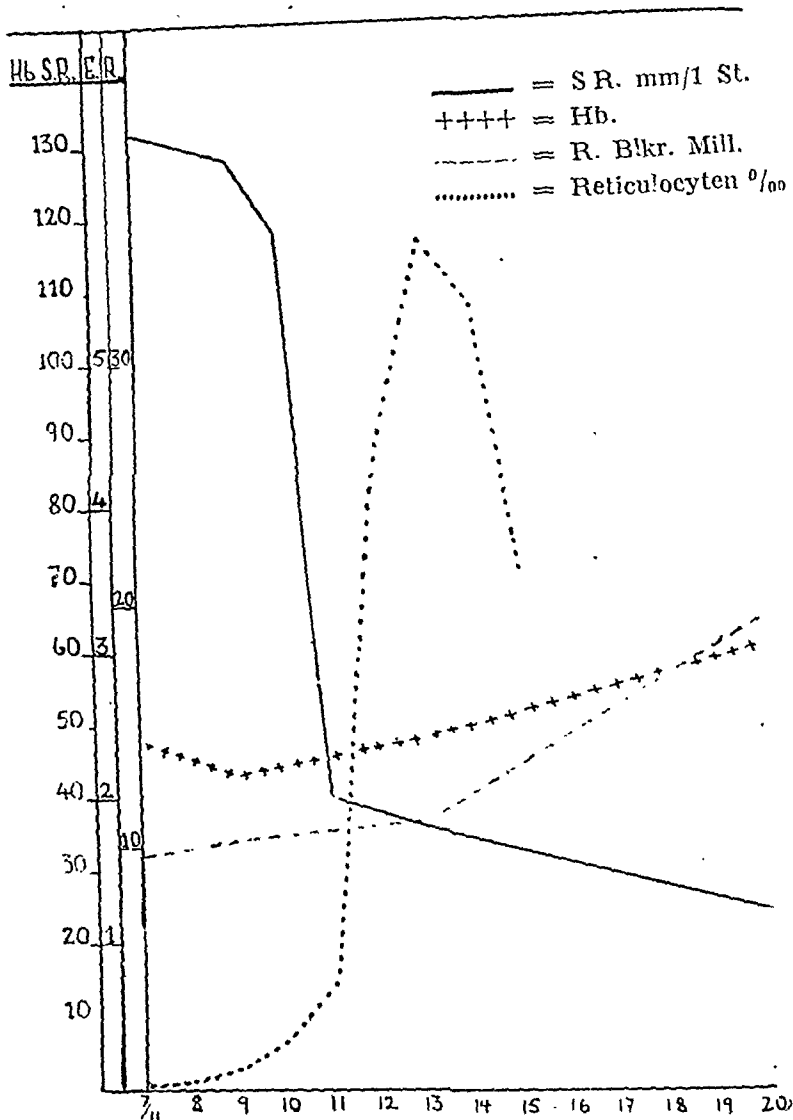


Fig. 3.

cithinzahl parallel damit zugenommen hat. In ein Paar Fällen hat eine Zunahme der S. R. während der Behandlung stattgefunden, (Fall 3 und 9), aber in diesen Fällen haben auch akute Infektionen eine Rolle gespielt und den Eiweissgehalt in so hohem Grade verändert, dass die S. R. davon beeinflusst worden ist.

Es ist ausserdem deutlich, dass eine negative Korrelation zwischen der S. R. und der Lysocithinzahl vorliegt. Begreiflicherweise ist dies Material zu klein, um auch nur mit einiger Sicherheit diesen Befund feststellen zu können, aber die Tendenz scheint mir

doch deutlich zu sein. Dieses ist am schönsten in Fall 2 zum Ausdruck gekommen, welcher in Fig. 2 graphisch gezeigt wird. Die Übereinstimmung zwischen den niedrigen Lysocithinzahlen und den hohen S. R.-Werten und umgekehrt geht klar aus dieser Tabelle hervor, und analog hiermit zeigt sich, dass die Fälle, die eine normale Lysocithinzahl haben, eine nur mässig erhöhte S. R. aufweisen.

Diese Kurven zeigen nach meiner Meinung instruktiv, dass die Eiweissverhältnisse des Plasmas *in diesem Fall* nicht das Geringste für die erhöhte S. R. bedeuten können. Ist doch die S. R. in diesem Fall, wo sowohl die Serumglobulin als auch die Fibrinogenmengen initial niedrig waren, und ausserdem von der ersten Untersuchung bis zur letzten *zugenommen* haben, vollständig unabhängig davon von 151 mm bis 20 mm heruntergegangen (nach Reduktion der Blutkörperchenzahl auf den ursprünglichen Wert.)

Der einzige, die Senkung beeinflussende Faktor, der sich zwischen den beiden Untersuchungen in erheblicher Weise geändert hat, ist also das Lysocithin, das in diesem Fall um das Vierfache *zugenommen* hat.

Um eine Auffassung darüber zu gewinnen, wie frühzeitig die Verminderung der S. R. während der Behandlung einsetzt, ist eine Anzahl von Fällen mit täglichen Kontrollen verfolgt worden. Diese Sache ist schon früher Gegenstand von Untersuchungen durch Reichel gewesen, der darauf hinweist, dass eine sehr schnelle Verminderung der S. R. als ein frühes und zuverlässiges Zeichen dafür eintritt, dass eine Remission wirklich in Gang gekommen ist. Reichel hat auch eine Reihe Kurven veröffentlicht, die dies beleuchten. Als Regel, meint er, kommt diese Senkungsverminderung gleichzeitig mit der Reticulocytenkrise. Er hebt auch hervor, dass, wenn eine Reticulocytenkrise auftritt, ohne dass die S. R. sinkt, der weitere Verlauf zeigt, dass eine wirkliche Remission nicht zu Stand gekommen ist. Nach einer erneuten intensiven Lebertherapie kann man später sehen, wie die S. R. sinkt und die Blutwerte *successiv* steigen. Dies betont auch Huo Cheng, der gefunden hat, dass die S. R. oft schon 24 Stunden nach dem Einsetzen der Behandlung heruntergeht. Er weist ausserdem darauf hin, dass die grosse Bedeutung der S. R. für eine Beurteilung der Wirkung der Behandlung nur dann eine wirkliche ist, wenn eine ursprünglich vorhandene sehr hohe S. R. schnell abnimmt. Diese

Ergebnisse kann ich zwar in allen Teilen bestätigen, muss aber betonen, dass die sehr schnelle Verminderung der S. R. in der Regel *vor* der Reticulocytensteigerung kommt, während zu gleicher Zeit die sog. Stabilisierungszahl (Berlin 1941) zunimmt. Siehe weiter Fig. 3. Aus diesem Grunde können sicherlich die zunehmenden Reticulocyten mit ihrer geringeren Aggregationsfähigkeit keine Rolle als ein die Senkung vermindender Faktor spielen.

Früher ist die schnelle Veränderung der S. R.-Werte Gegenstand der verschiedenartigsten Auslegungen gewesen. Als Versuch zu einer Erklärung hat man z. B. den Umstand angegeben, dass die CO₂-Bindungskurve des Blutes sich im Anfang der Remission verändert, schon ehe die Hämoglobinkonzentration eine Veränderung nach oben erfahren hat (Hitzenberger und Tuchfeld). Muller hat gemeint, dass die Tatsache dass das Blutcholesterin in einigen Fällen gleichzeitig mit der Reticulocytenkrise schnell zunimmt, für die Erklärung der sinkenden S. R. von Bedeutung sein könnte. Wie oben erwähnt wurde, hat man von mehreren Seiten die Ansicht vertreten, dass die jungen Reticulocyten eine geringere Aggregationstendenz hätten als die reifen Blutkörperchen, und dass die S. R. teilweise aus diesem Grunde abnimmt. Dies ist zwar richtig, führt aber zur Entstehung einer sog. Schleiersenkung von typischem Aussehen (Gripwall).

Aus der Tatsache, dass diese Abnahme der S. R. schon vor der Reticulocytenkrise eintritt und dass man durch Austauschversuch mit normalen Blutkörperchen keine Veränderung in der Senkungsgeschwindigkeit feststellen kann, geht nach meiner Auffassung hervor, dass der einzige Umstand von Bedeutung für das Verständnis dieser Verhältnisse derjenige ist, dass der Lysocithingehalt rasch zunimmt, nachdem man eine wirksame spezifische Behandlung eingesetzt hat. Ebenso düften sich die sehr hohen Senkungswerte, die man in einigen Perniciosafällen findet, dadurch erklären lassen, dass hierbei der Lysocithingehalt im Plasma wesentlich vermindert zu sein pflegt, und folglich eine erhöhte Münzrollenbildung zu Stande kommen kann.

Zusammenfassung.

Nach einer Litteraturübersicht, die die Tatsache beleuchtet, wie wenig eigentlich über die Ursachen für die bei perniziöser Anämie oft extrem erhöhte S. R. bekannt ist, abgesehen von der Bedeutung, die der verminderten Blutkörperchenzahl zukommt, geht der Verfasser auf eine Serie eigener Versuche über. Es wird nachgewiesen, dass in den Fällen von Perniciosa, wo die S. R. stark erhöht ist, ein bedeutend herabgesetzter Lysocithingehalt im Plasma vorliegt. Versuche mit Parallellbestimmungen von Fibrinogen, Serumglobulin, Albumin und Lysocithin mit gleichzeitiger Messung der S. R. in 10 Fällen von Perniciosa zeigen, dass die Eiweissverhältnisse in den untersuchten Plasmaproben wahrscheinlich sehr wenig für die Erklärung der Senkungszunahme zu bedeuten haben. Diese sind nämlich in praktisch allen Fällen normal oder subnormal. Von den 10 Fällen sind 8 mit sämtlichen erwähnten Bestimmungen auch nach effektiver spezifischer Behandlung weiter verfolgt worden und es hat sich gezeigt, dass das einzige, das sich im Laufe der Behandlung wesentlich geändert hatte das Lysocithin war; so hat dieses z. B. in einem Fall bis zum Vierfachen zugenommen, während sich die Eiweissfraktionen in keinem höheren Grad geändert haben. Gleichzeitig hiermit ist die S. R. von 151 mm bis 20 mm gesunken.

Zum Schluss wird hervorgehoben, dass diese in der Regel rasche Verminderung der S. R. vor der Reticulocytenkrise eintritt, während zu gleicher Zeit eine Zunahme der sog. Stabilisierungszahl festzustellen ist und demnach das Perniciosaplasma während der Behandlungsdauer seine Fähigkeit, Lysocithin zu bilden, zurückerhält.

Der Verfasser ist der Ansicht, dass die Versuche es in hohem Grade für wahrscheinlich erscheinen lassen, dass der verminderte Lysocithingehalt des Plasmas bei perniziöser Anämie die Ursache für die oft erhöhte S. R. bei dieser Krankheit ist.

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Investigations on Serum Albumin and Urine Albumin during Proteinuria.

By

MOGENS FABER.

(Submitted for publication July 8, 1943).

The study of the proteinuria in kidney diseases has, especially in the past, given rise to considerable discussion regarding the origin of the urine protein. Numerous investigators have studied the relation between serum protein and urine protein, and even though the results frequently have been conflicting they seem more recently to point to the fact that the two proteins are identical. There is not complete agreement, but a few of the newer publications apparently offer an explanation of any discrepancies that may exist. (As regards pertinent literature, reference is made to the monograph by Bing).

Goettsch and Reeves were able to show that in patients with nephrosis it was impossible to precipitate all the serum protein in an otherwise quantitative precipitation with anti-sera prepared with normal serum protein, finding in these patients a smaller precipitation than corresponding to a determination based on Howe's salting-out technique. In normal dogs, however, it was possible to precipitate all the serum protein by this method. In a later paper Goettsch and Lyttle have gone further into the question, having a larger material on hand. In severe cases of nephrosis it was frequently but a smaller amount of albumin as well as globulin

which could be precipitated, while a larger fraction remained in solution. When the nephrosis improved the abnormal protein fractions diminished at the same time, though the change here was slower than the improvement in oedema and proteinuria. Similar changes were found also in patients with nephritis, but as a rule less pronounced, even though here too maximum changes could be found. In contrast to the albumin the abnormal globulin could form antiserum and could therefore be precipitated independently. The urine was also found to contain these abnormal proteins, though in smaller amounts. The investigation failed to establish any connection between the magnitude of the proteinuria and the amount of abnormal protein, even though the latter was found far more frequently in the larger proteinurias.

Investigations giving similar results have been published by Alving and Mirsky who investigated the cystine content of serum albumin. In patients with nephrosis they found less cystine in the serum albumin than in the urine albumin, and, moreover, that the latter contained as much cystine as did normal serum albumin. In contrast, the globulin was found to be unchanged. In a single case they succeeded in separating a new protein from the serum albumin, the protein being insoluble in salt-free liquid. The cystine content of this new protein proved to be considerably less than that of either albumin or globulin.

These particular results seemed so interesting that they have been made the subject of further investigation.

The cystine content of serum is not reported alike in the literature. Thus Lang and Braun found 5.2 % in the purest fractions, Tuchman and Reiner an average of 6.07 % with variations from 5.35 to 7.40 %, and Balint and Balint $4.99 \% \pm 0.25 \%$ for the whole of the albumin fraction and a little more, 5.03 %, for the part that remained in solution at 30 % ammonium sulphate.

Technique.

Serum is obtained after coagulation of blood secured without addition and independently of meals, as a rule in the forenoon. This serum is diluted with equal parts of water, and 1/10 volume of sodium acetate/acetic acid buffer is added according to Henriques and Klausen. The globulin is precipitated from this mixture

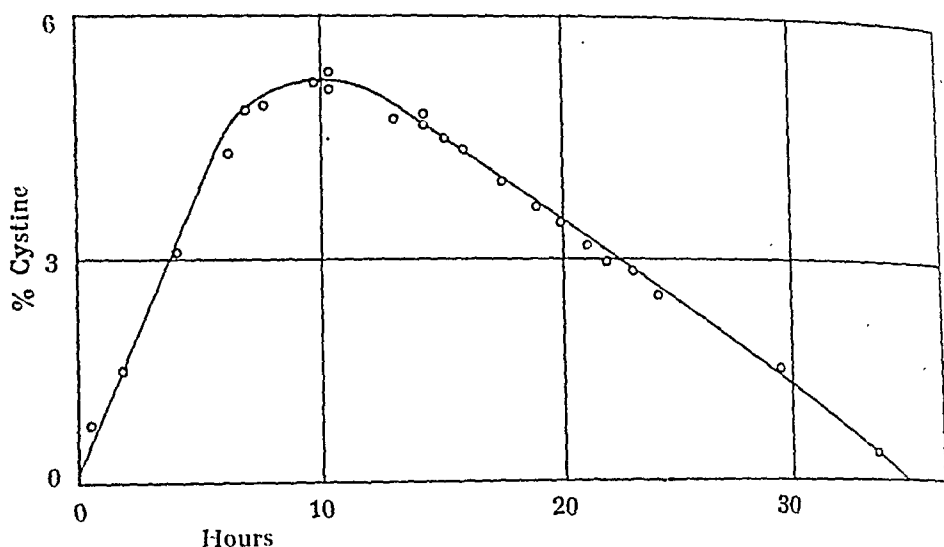


Fig. 1.

The measurable amount of cystine during hydrolysis of serum protein.

by addition of equal parts of saturated solution of ammonium sulphate. The precipitate is isolated and dissolved in the smallest possible amount of water. 10 ml of saturated ammonium sulphate are added, thereupon concentrated hydrochloric acid (generally about 0.25 ml) until no further precipitate is formed. The precipitate is filtered and dissolved in the minimum amount of water. With 10 ml of serum to start with, 25 ml of water will usually be required for the solution of the globulin and 50–100 ml for the solution of the albumin. The urine is treated in the same manner after filtration and neutralization, but without any dilution.

In the solutions thus prepared protein is determined as nitrogen by the micro-Kjeldahl method. First, however, the protein is precipitated with tannic acid and the precipitate washed with a dilute solution of tannic acid until free from ammonium sulphate.

In the protein solution formed cystine is determined after hydrolysis with hydrochloric acid. 0.3 ml of the protein solution is transferred to a 100 ml flask with 17 ml of concentrated hydrochloric acid so that the final concentration is 20 % HCl. The flask is equipped with condenser and the mixture is boiled for 9½ hours on electrically heated sand bath. Hydrochloric acid is now evaporated until the mixture has the consistency of syrup, and the residue is transferred to a 20 ml measuring flask where it is neutralized with sodium hydroxide, using methyl red paper as an indicator,

until pH=about 5.7. The contents are made up to 20 ml and filtered. Cystine is then determined according to Kassel and Brand, without modification, though the author finds a slightly different extinction curve.

During the hydrolysis the cystine is subject to a continuous breakdown so that values found after the hydrolysis undoubtedly are not entirely correct. We have therefore checked, by constant sampling, the amount of cystine that can be determined during the hydrolysis of a serum protein preparation. The cystine content

Table 1.

The cystine content of serum proteins in normal persons.

Albumin, cystine %		Globulin, cystine %
1	2	
1. 4.52—4.57	4.47—4.42	1.75—1.75
2. 4.52—4.63	4.69—4.73	1.62—1.72
3. 4.31—4.26	4.49—4.42	2.14—2.02
4. 4.82—4.90	4.82—4.82	1.56
5. 5.37—5.49	5.21—5.18	2.34—2.28
6. 4.33—4.40	4.28—4.28	1.92—1.92
7. 5.21—5.21	5.21—5.21	2.00—2.04
8. 4.72—4.72	4.45—4.45	1.92—1.98
9. 4.93—5.04		1.96—2.08
10. 4.47—4.33		2.13—2.09
11. 4.65—4.65		1.72—1.81
12. 4.65—4.73		2.06—1.96

of the hydrolysate is shown in fig. I. It will be seen that the curve displays a rather rapid rise until reaching, in about 10 hours, a maximum zone extending over a couple of hours. Then follows a linear drop in the amount of cystine. 10 hours has therefore been chosen as the best time of hydrolysis. The true value of the cystine content of the hydrolyzed protein is undoubtedly higher than the value at 10 hours and must be situated between this value and a value corresponding to the point where the extension of the rectilinearly falling part of the curve will intersect the ordinate.

The accuracy of the method is shown in table 1, giving double analyses on a single hydrolysate as well as analyses on two hydrolysates. The accuracy appears to be about $\pm 5\%$.

Table 2.

The cystine content of the serum and urine proteins from patients with proteinuria.

Diagnosis	C y s t i n e % i n			
	S e r u m		U r i n e	
	Albumin	Globulin	Albumin	Globulin
Proteinuria below 1 g per 24 hours.				
Pyelonephritis	4.53	2.50		
Pyelonephritis	5.19	2.50		
Pyelonephritis	3.70	2.14		
Proteinuria above 5 g per 24 hours.				
Nephrosis	1.99	2.02	4.38	2.19
Nephritis chron. ..	2.07	1.97	4.55	1.86
Nephritis chrcn. ..	3.33	2.68	5.01	1.96
Nephrosis	3.53	1.60	5.14	1.93
Nephritis chron. ..	3.15	2.03		2.04
Nephrosis	1.74	2.24	5.10	2.17
Nephropathia of pregnancy.				
1.	5.05	2.31		
2.	4.60	1.73	4.79	1.89
3.	4.16	1.96	4.41	1.81

Results.

The normal material, comprising 12 determinations, shows in case of the albumin fraction a cystine content varying from 4.28 to 5.49 %, with an average of 4.75 %. In case of the globulin fraction the cystine content is found to vary from 1.56 to 2.34 %, with an average of 1.95 %. These results are in good agreement with those obtained by earlier investigators.

The situation is entirely different in case of patients with diseases of the kidneys. Table 2 shows that in the majority of such cases we find a reduction of the cystine content of the serum albumin, a reduction so large that a few of the protein samples examined contain less than half of what is normally found. In contrast to this finding the urine albumin samples show a normal cystine content. Serum globulin and urine globulin, however, show in all instances normal cystine content.

The reduction in the cystine content of the serum is to some degree dependent on the magnitude of the proteinuria. In mild proteinuria, i.e., with less than 1 g of protein per 24 hours, we

find only insignificant deviations from the normal. In severe proteinuria, *i.e.*, more than 5 g in the diurnal urine, and in most cases more than 10 g, a reduction is always observed. The duration of the proteinuria is likewise of importance. The short, but usually violent proteinuria of nephropathia of pregnancy gives only a rather insignificant reduction of the cystine content.

Thus it appears that the difference found between the cystine contents of serum albumin and urine albumin is essentially dependent on the proteinuria. This phenomenon seems most readily explained by means of the above mentioned experiment by Alving and Mirsky in which these investigators succeeded in isolating an abnormal protein in the serum albumin fraction.

When dialyzing a solution of serum albumin from a patient with proteinuria for a sufficient length of time a precipitate will appear, at any rate when the proteinuria is reasonably pronounced. The author has carried out such dialyses, using collodion caps. When the outer liquid was changed daily a week would usually have elapsed before the precipitate appeared. When it just began to appear it might be redissolved by dilution, but the next day it was completely insoluble. Dialysis of 4 albumin samples from normals gave no precipitate, even when the dialysis was continued beyond a week. Table 3 shows the result of such experiments on serum from patients with proteinuria. In all cases investigated it

Table 3.

Diagnosis	Total Protein g pr 100 ml serum.	Serum Albumin						Urine Albumin Cystine %	Serum Globulin		Urine Globulin Cystine %
		Total Albumin		Solub. Alb. Fract.		Insol. Alb. Fract.			g. pr 100 ml. serum	Cystine %	
		g. pr 100 ml. serum	Cystine %	g. pr 100 ml. serum	Cystine %	g. pr 100 ml. serum	Cystine %				
Nefros. Amyloid.	3.03	1.06	2.18	0.92	2.87	0.68	0.92	2.65	1.97	2.00	1.69
Same	3.21	1.39	2.05	0.45	2.70	0.94	0.70	2.70	1.92	2.04	1.99
Chron. Nephritis	5.32	0.63	3.40	0.44	4.38	0.19	0.82	4.31	4.69	2.11	1.92
Chron. Nephritis	5.06	2.55	1.91	0.78	4.86	0.67	0.52	3.82	2.45	1.89	2.08
Nefros. Amyloid.	4.96	2.04	1.85	1.02	2.97	1.02	0.73	3.15	2.92	2.17	1.85
Nefros. Amyloid.	4.34	1.57	2.06		2.94			3.15	2.77	1.95	1.85
Nefrosis	6.95	3.31	3.14	1.76	5.10	1.55	0.82	4.59	3.64	1.95	1.99
Chron. Nephritis	7.59	2.51	3.77	1.87	4.79	0.64	0.71	5.02	5.08	2.04	1.81

was possible to demonstrate the presence of this protein characteristic for such patients, and in several cases it constituted more than half of the total albumin fraction.

The precipitated protein seems to be denatured. At any rate, it cannot be dissolved again in salt solutions or after pH-changes. The chemical composition of the precipitated protein is entirely different from that of normal serum albumin. While the cystine content of the normal albumin is about 4.75 %, the precipitated protein contains between 0.5 and 0.9 %. As it undoubtedly is contaminated by serum albumin it is safe to assume that the lowest value is the most correct. It also corresponds with the findings of Alving and Mirsky in the case investigated by them. The nitrogen content of the protein in question is in two samples found to be 14 and 14.1 % respectively.

The protein which remains in solution after the dialysis appears to have the same composition as the albumin in normals, at any rate as far as the cystine content is concerned. An exception is the albumin in the cases with amyloidosis investigated, but these cases will be treated separately. All the samples of urine examined contain an albumin which resembles the normal protein, but the method of determination is not sufficiently accurate to eliminate the possibility that a smaller amount of protein might be present in the urine albumin without it being possible to detect it in the cystine determinations. Thus it will be seen that most of the urine albumins contain a little more cystine than the corresponding serum albumins. This is presumably due to the presence of diffusible nitrogen-containing substances and not the presence of the cystine-poor protein. In 4 of the cases investigated dialysis gives no precipitation which might indicate an admixture of this protein. The dialysate, however, shows a fall in the nitrogen content while the cystine content is constant. This phenomenon has then produced an apparent rise in the cystine content of the dialysate.

Discussion.

It has been shown that serum in patients with proteinuria contains a protein which is precipitated by ammonium sulphate in the albumin fraction, but is insoluble in salt-free liquid — a protein which in its chemical composition deviates from both albumin

and globulin in normals, and which does not pass out into the urine during the proteinuria.

It does not seem very probable that this protein is found in normals, at any rate it is not present in any large amount. The cystine content of normal albumin and of the soluble part of the albumin from patients with proteinuria is the same, and no precipitation is observed even in prolonged dialysis of normal serum albumin. Very small amounts, however, will hardly manifest themselves in the cystine determinations and may perhaps not be precipitated either, so the question of the presence in normal albumin is not answered with absolute certainty. If such small amounts were present, the rise during the proteinuria would presumably have the same origin as the rise in choline esterase concentration under similar conditions. It is another possibility that this protein is produced during the proteinuria as an attempt on behalf of the organism to preserve the colloids in plasma.

It seems as if the cystine-poor protein here mentioned must be found in the protein described by Goettsch and co-workers, which they were unable to precipitate by means of anti-sera. Altogether, the two proteins seem to accompany each other during the development of the disease — but it is doubtful that they are completely identical since Goettsch also finds some of his protein in the urine, though less than in serum. While not completely identical, the one described here may be included in the protein described by Goettsch.

It is strange that none of these protein groups can be rediscovered as independent protein in electrophoresis experiments. In such experiments we find, as shown by Luetscher for example, only an increased amount of β -globulin and, if the albumin content is very low, an increased amount of α -globulin. The behavior of the albumin appears natural. At $\text{pH} = 4$ the albumin may be separated into 2 fractions, but both of these pass through the kidneys with their mutual ratio unchanged.

Summary.

In a number of cases of proteinuria the cystine content of the serum albumin is found to be considerably reduced. Moreover, it is found that this reduction is due to the presence of a protein having a very low cystine content. This protein cannot be demonstrated to be present in normal persons, and does not pass out into the urine. It does not seem to occur in patients with proteinuria until this proteinuria has reached a certain magnitude and has lasted for some time. The most reasonable explanation of the accumulation of this protein during proteinuria is that it is normally found in very small amounts and first during proteinuria is retained and increased in amount while the rest of the serum albumin passes out into the urine.

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Serum Choline Esterase in Patients with Proteinuria.¹

By

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(Submitted for publication July 8, 1943).

In earlier papers (Faber) it has been shown that there exists a definite correlation between the serum choline esterase and the serum albumin, so that low concentrations of the albumin follow low values of the serum choline esterase and high albumin concentrations are found in patients exhibiting high values of the serum choline esterase, a straight line reaction existing between the two substances. These observations are best explained by attributing the same origin to the two serum proteins in question, the place of formation presumably being the liver. A few simple deviations from the rule have been pointed out.

In view of these observations it seemed natural to investigate the behavior of the serum choline esterase in case of the exceedingly low values of the serum albumin which are found in proteinuria caused by diseases of the kidney. In this investigation the choline esterase determinations were made according to the gasometric technique of Ammon, 1 % serum and 0.8 % acetylcholine chloride being used. The temperature was 38° C. The amount of CO₂, in cubic millimeters, evolved in 60 minutes is a measure of the number of units of choline esterase. For details, see earlier papers.

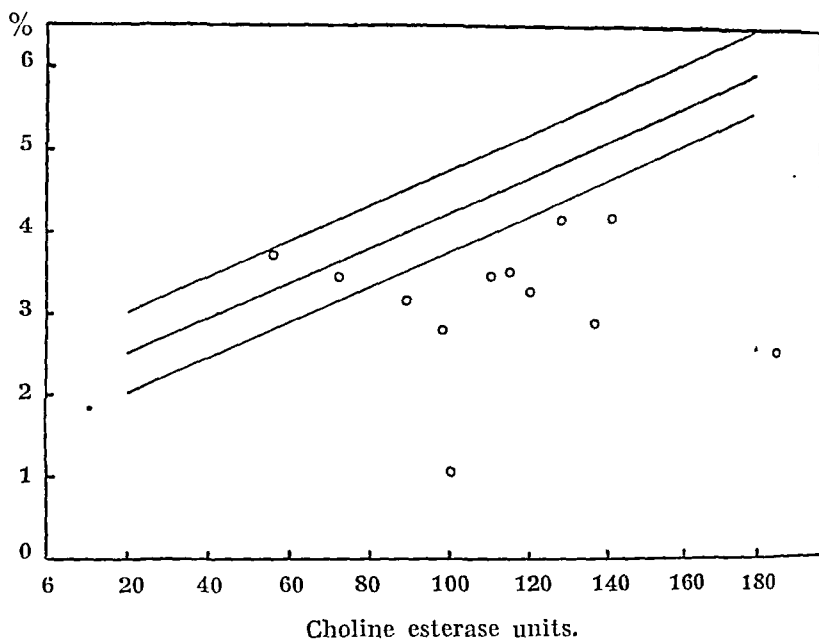
¹ Aided by a grant from Nordisk Insulin Fond.

The protein analyses were made according to the method of Henriques and Klausen, the nitrogen determinations according to A. C. Andersen and Norman Jensen.

The correlation between the serum choline esterase and the serum albumin previously found was not observed in patients with proteinuria. Rather, the relationship was reversed, so that

Serum
Albumin

Fig. 1.



The ratio between serum choline esterase and serum albumin in cases with proteinuria. The middle one of the lines in the graph is the average line drawn from cases without proteinuria. The two other lines represents a variation of $\pm 0.5\%$ albumin. 80 % of the cases without proteinuria are found inside this limit.

the patients showing the lowest concentrations of serum albumin frequently exhibited the highest values of serum choline esterase. Fig. 1 shows the first determinations in case of all patients examined. It will be seen how most of the determinations deviate, often to a considerable degree, from the region marked off in the graph by the lines within which the values for 85 % of the patients without proteinuria were found to be located (see earlier paper by Faber).

Table 1.

Serum choline esterase in patients with proteinuria.

No.	Sex	Age	Diagnosis	Date	Choline esterase units	Total serum protein %	Albumin %	Serum globulin %	Proteinuria %	Diuresis cc	Approximate protein secreted per day gr.
1	M	49	Nephrosis amyloid.		186	5.27	2.53	2.74			
2	F	22	Pyelonephritis in puerp.		141	7.20	4.18	3.02	0.125		
3	M	34	Nephritis chronica	5.XII	137	4.93	2.90	2.03	0.3	1150	3.5
				8.XII	129	5.05	2.69	2.36	0.3	1350	4.1
				11.XII	138	4.99	2.98	2.61	0.6	2150	12.9
4	F	30	Nephritis		128	6.25	4.14	2.11	0.15	1050	1.5
5	M	29	Nephritis chron.		120	5.43	3.27	2.16	0.5	1150	5.8
6	F	46	Pyelonephritis		115	6.04	3.50	2.54	0.04	1020	0.4
7	F	38	Nephritis chron. Uremia	12.XI	110	5.81	3.48	2.32	0.15	1200	1.8
				6.XII	117	5.72	3.56	2.16	0.1	1600	1.6
				13.XI	123	6.20	3.52	2.68	0.15	800	1.2
8	M		Nephrosis		100	4.44	1.07	3.57			
9	F		Eclampsia		98	5.32	2.76	2.56	1.2	880	10.6
10	M	88	Nephritis chronica		89	6.38	3.19	3.19	+		
11	M	47	Nephritis chronica		72	7.40	3.44	3.95	0.03		
12	M	39	Nephritis chron. Uremia		56	5.92	3.72	2.20	0.17	1000	1.7

Table 1 shows a record of all determinations made on patients with proteinuria, though only the first determination for the patients whose cases will be discussed individually.

In these cases we thus find a separation of the courses followed by the concentrations of albumin and choline esterase in the serum. In nearly all instances this separation is found to depend on the circumstance that the choline esterase value is higher than one would expect according to the concentration of the serum albumin.

The natural place for this separation to occur would presumably be the kidney, and so it is found to be. An investigation of 8 specimens of urine which did not contain protein in demonstrable amounts failed to show the presence of choline esterase. Conditions were different in case of protein-containing specimens of urine, as shown in table 2.

Table 2.
Secretion of the choline esterase in the urine.

No.	Diagnosis	Serum choline esterase units	Serum albumin %	Urine choline esterase %	Urine total protein %	Urine albumin %	Urine globulin %	Urine choline est. Serum choline est. $\times 10^{-3}$	Urine alb. Serum alb. $\times 10^{-3}$
1	Nephrosis amyloid.	170	1.94	3.3	0.59	0.27	0.22	1.94	13.9
3	Nephritis chronica	129	2.69	3.4	0.39	0.33	0.06	2.63	12.3
5	Nephritis chronica	130	1.64	5.5	0.43	0.27	0.16	4.23	16.5
8	Nephrosis	99	1.18	2.7	1.14	0.54	0.60	2.72	45.7

All these specimens of urine contained small, but clearly demonstrable amounts of choline esterase. Prior to the determinations all specimens were dialyzed for 48 hours against distilled water to remove most of the salts which otherwise might interfere with the analyses. Owing to the small amounts of choline esterase all determinations in urine were carried out in 5 % or 10 % dilution in order to obtain definite manometric deflections, but the results were then converted on the basis of the 1 % dilution usually employed. The table shows that the urine investigated contains but a small amount of choline esterase. Thus No. 1 in table 2 contains only 3.3 units of choline esterase, while the serum contains 170 units. The urine thus has a concentration corresponding to only 2 % of what is found in serum. In contrast we find a serum albumin of 1.94 %, simultaneously with an albumin percentage in the urine of 0.27. This means that while the albumin concentration of the urine is 15 % of that of the serum, the corresponding figure for the choline esterase is only 2 %. This difference would be still more striking if we took into account that a substantial part of the albumin fraction does not at all pass out into the urine (Faber). Thus the secretion of albumin in the urine is considerably larger than that of choline esterase. That we here have the explanation of the above mentioned phenomenon is also evident from the following cases which include an investigation of the magnitude of the proteinuria.

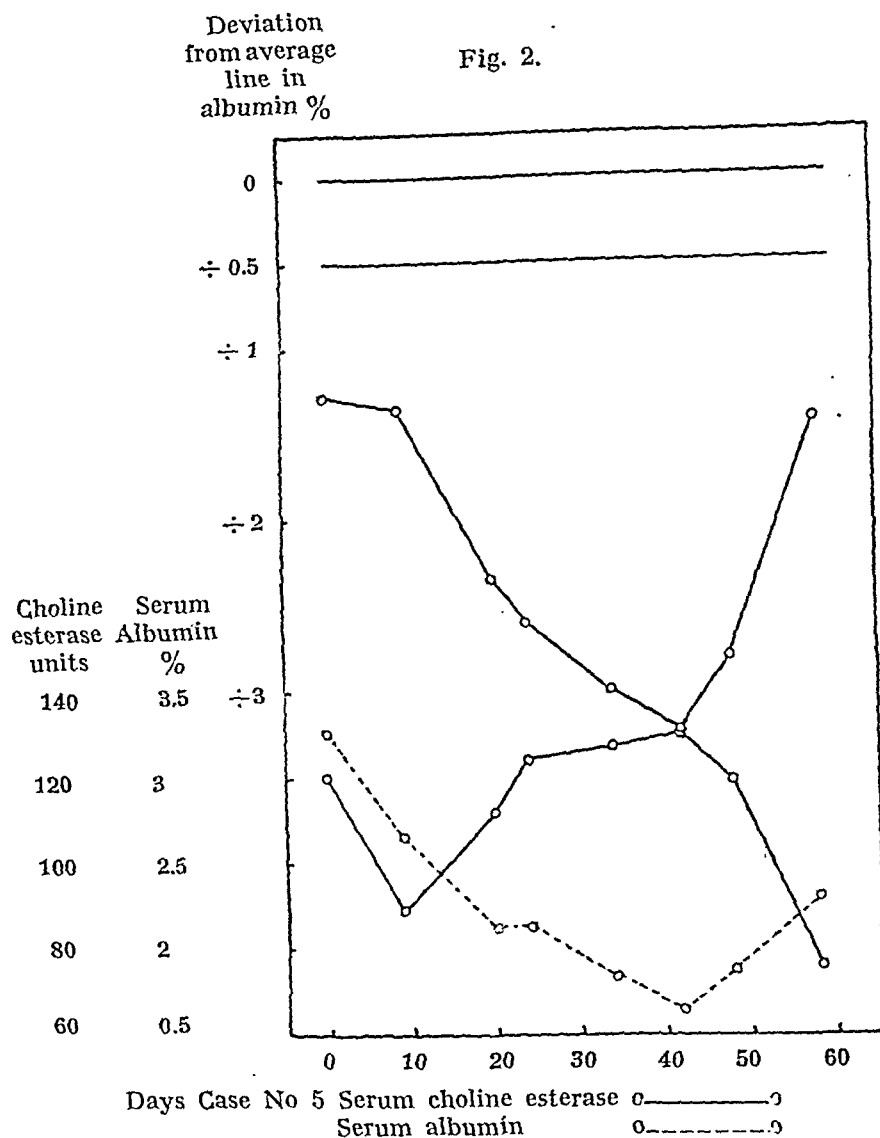
Case 5.

A man aged 29 years.

Diagnosis: Nephritis chronica.

From the journal: Previously always of good health. The present ailment began 10 days before admission, with cold, coughing and hoarse-

Fig. 2.



The investigations on protein and choline esterase in serum are recorded in table 3 and fig. 2.

Table 3.

Determinations of choline esterase and protein in serum Case 1.

Date	Choline esterase units	Total serum protein %	Serum albumin %	Serum globulin %	Esbach	Diuresis	Approximate protein secreted per 24 hours g
30/9	120	5.43	3.27	2.16		900	
3/10					5	1150	5.8
9/10	89	4.70	2.65	2.05	6	1550	9.3
17/10					5	1450	7.2
20/10	112	4.51	2.15	2.36		1400	
23/10					6	1350	8.1
24/10	124	4.66	2.15	2.51		1350	
31/10					5	1250	6.2
3/11	127	4.06	1.82	2.24		1000	
7/11					7	1100	7.7
11/11	130	4.07	1.64	2.44		1050	
14/11					7	700	4.9
17/11	119	4.47	1.85	2.62		800	
27/11	76	5.05	2.30	2.75	7	300	2.1

Comment: This is a typical case of nephritis with uremia. During the period observed the proteinuria seems to have increased at first, then to fall towards the end. Under these conditions we find in the beginning a fall in the serum albumin concentration. This fall is accompanied by a rise in the serum choline esterase, so that the ratio between the two substances departs considerably from the expected value. Associated with the falling proteinuria at the end of the period of observation we find once more a rise in the serum albumin concentration towards normal values, but this time accompanied by a fall in the choline esterase value so that we again approach the average line.

Case 9.

A woman aged 20 years.

Diagnosis: Partus, nephritis, eclampsia.

From the journal: Previously of good health. The urine contained no albumin 10 days before admission. For 8 days prior to admission the patient suffered increasing headache. Oedema developed in the face.

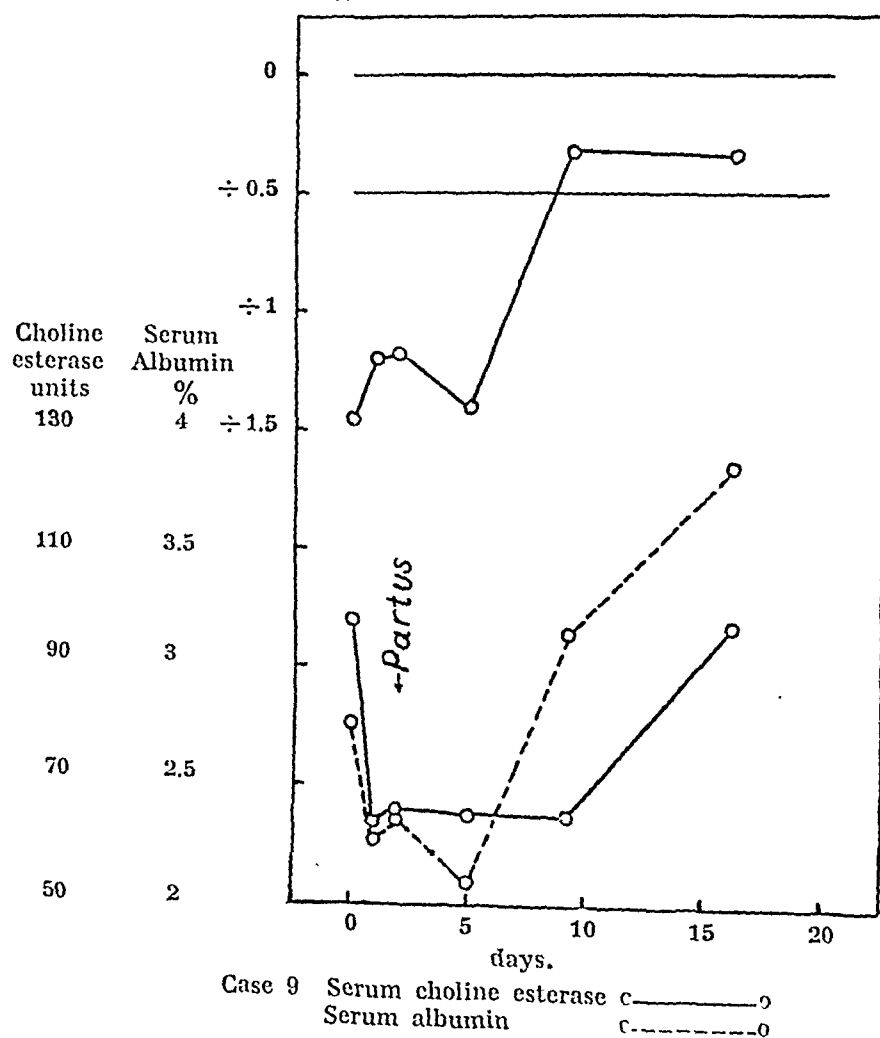
Table 4.

Determinations of choline esterase and protein in serum. Case 2.

Date	Choline esterase units	Total serum protein %	Serum albumin %	Serum globulin %	Esbach	Diuresis	Approximate protein secreted per 24 hours g.
27/5	98	5.32	2.76	2.56	1.2	880	9.6
28/5	64	4.65	2.27	2.38	0.3	650	2.0
29/5	66	4.65	2.37	2.28	0.4	1800	7.2
1/6	65	4.65	2.10	2.55			
5/6	65	5.95	3.16	2.79	Trace	700	
12/6	97	6.98	3.84	3.14	Trace	600	

Deviation
from average
line in
albumin %

Fig. 3.



The night before admission dimmed vision increasing to almost complete blindness. Shortly before being admitted to the hospital the patient suffered a typical eclamptic attack, and another attack at admission. B.p. 190/145 upon admission.'

The patient was treated ad modum Stoganoff, and cleared up in the course of the first 24 hours. The vision became normal in a couple of days, and birth took place after two days. The childbed was without complications. Investigations of the choline esterase are recorded in table 4 and fig. 3.

Comment: A patient with proteinuria of short duration due to eclampsia shows immediately a decrease in the serum albumin concentration. This decrease is accompanied by a fall in the serum choline esterase value, but even at the lowest choline esterase value the albumin/choline esterase ratio shows a distinct displacement in favor of the choline esterase. When the proteinuria suddenly stops, a rise in the serum albumin concentration is observed, with the result that the ratio between albumin and choline esterase increases to within less than 0.5 % albumin from the average line, without any simultaneously occurring change in the choline esterase value. During the time that follows we observe a rise in the values for both substances investigated, so that the ratio between them proceeds parallel with the average line.

Discussion.

These investigations show that the ratio between albumin and choline esterase in serum will remain rather constant as long as the proteinuria is constant, but at a level displaced in favor of the choline esterase (cases no. 3 and 7.) Case No. 5 shows how a fall occurs in the serum albumin concentration at the same time as the proteinuria increases. This fall, however, is not accompanied by a simultaneous fall in the serum choline esterase value, as found in patients without proteinuria, but is on the contrary accompanied by a rise in the choline esterase value. On the other hand, when the proteinuria stops abruptly as in case No. 9 we soon observe a rise in the serum albumin concentration, but a rise in the serum choline esterase does not follow until the albumin concentration has reached almost normal values.

Of special interest is the case where the proteinuria falls towards the end — as illustrated in case No. 5. It will be seen how there

is a rise in the serum albumin concentration, but now accompanied by a fall in the serum choline esterase value, so that the ratio between the two substances approach the average line, but apparently in a manner which is somewhat different from what we found in case of the total discontinuance of the proteinuria in case No. 9. Conditions similar to those of case No. 5 are presumably also found in case No. 12. Here we find an albumin/choline esterase ratio which lies close to the average line as if it were a case of a patient without proteinuria. Here too the determination was made shortly before death, the patient dying within 24 hours after the sample was obtained.

Thus it appears that it is the proteinuria which in these cases essentially is responsible for the displacement found in the ratio between albumin and choline esterase, and that most of the variations in this ratio are intimately associated with variations in the proteinuria.

No explanation can be given of why the choline esterase does not accompany the albumin through the damaged kidney membrane. The size of the choline esterase molecule is not known. Choline esterase is salted out of serum in the same way as the serum albumin, and this circumstance would indicate that the molecular size is the same for the two substances. It should be added, however, that Vahlquist has shown that the choline esterase in cataphoresis experiments migrates independently of both albumin and globulin, so that the deviating charge perhaps may offer an explanation of the phenomenon in question.

There are other indications that the serum choline esterase is disinclined to pass the capillary membrane. Thus one of the cases examined — that of severe ascites — shows approximately the same albumin/choline esterase ratio in serum as that found in proteinuria. The case in question was one of liver cirrhosis where a large ascites was constantly produced so that it was necessary to tap the fluid every 20th. day. Here the serum showed a choline esterase value of 70 simultaneously with a serum albumin content of 2.50 % where according to previous findings one should expect 3.40 %, thus a displacement in the same direction as in proteinuria. In the ascites an albumin content of 0.55 % was found together with a choline esterase of 8.5, thus only half as much choline esterase in proportion to the albumin as found in the serum.

What is said here supports the idea that the albumin and the choline esterase have a common place of origin and that they are dependent on each other in their rate of formation. When the formation of albumin is increased owing to proteinuria, more choline esterase will also be formed. It is retained in serum and the concentration increases. When the proteinuria declines there is presumably also a fall in the rate of formation of the albumin, and the choline esterase will likewise show a fall.

Summary.

In serum from patients with proteinuria we observe a displacement away from the normal ratio between albumin and choline esterase so that the concentration of the latter shows a rise, this rise being the bigger the greater the amount of urinary albumin. This accumulation of choline esterase is presumably due to a smaller urinary loss compared with the bigger loss of albumin. at the same time as the ratio between the rates of formation of the two substances remains constant, probably on account of common place of origin.

Litteratur.

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Experiments in the Determination of Thiamine in Urine with Chemical Methods.

By

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In consideration of the extent to which the B-vitamins, especially thiamine, are now used in therapeutical practice, and of the often extremely vague and ambiguous symptoms and therapeutical results that have been adduced in cases of suspected lack of thiamine, it is clear that an exact method of determination of thiamine in the blood, urine and other biological fluids would be of great value. A large number of such methods have also been published. In order to get some idea of their reliability I have tested out a couple of them where the procedure described seemed acceptable and the results given were good. My own results, however, have been negative, as they have shown that the thiochrome methods for urine that I made the subject of my tests only allowed of a rough estimation of the thiamine content.

The laboratory possibilities with which for the present we can tackle the thiamine problem are of two kinds — indirect and direct methods of determination.

In the first case one determines substances that arise intermediately during carbohydrate conversion, e. g. pyruvic acid and there-with related compounds that in cases of impaired carbohydrate conversion due to lack of thiamine accumulate in the blood or show increased excretion in the urine. For the determination of these substances satisfactory chemical methods have been worked out

(Case 1932, Lu 1939, Bueding and Wortis 1940, Högborg and Schlenk 1940, Klein 1941 and others), and a number of investigations, including also some from Scandinavia (Carlström, Holmin and Myrbäck 1939, Hammarsten 1942, Porjé 1942 and others) have been published. The disadvantage of these methods is that an increase in pyruvic acid or an increase in bisulphite-binding substance does not give an unequivocal and still less a conclusive indication of lack of thiamine as the cause, which is, of course, quite natural, as the pyruvic acid is of central importance not only in connection with the carbohydrate conversion but also with the conversion of fats and proteins. Thus, increases in pyruvic acid have been shown in connection with physical exercise (Lu and Platt 1939), diabetes (Möllerström 1941), hepatites (Hammarsten and Ståhle 1942) as well as experimentally in A- and D-avitaminotic rats with an ample supply of B-vitamin (v. Euler and Högborg 1940) etc. Nor, it would seem, is it possible *ex juvantibus* to prove lack of thiamine to be the cause of increase in pyruvic acid, since a pyruvic acid-decreasing effect of thiamine has been demonstrated also in case of pyruvic acid increase from other causes than lack of thiamine, e.g. A-avitaminosis (v. Euler and Högborg 1940) as well as in healthy human subjects with normal pyruvic acid values.

It would thus appear that the only conclusion to be drawn from a heightened pyruvic acid value is that lack of thiamine *may* exist. A normal value, on the other hand, speaks rather definitely against lack of thiamine; but one cannot with absolute certainty exclude the possibility of a mild lack without pyruvic acid increase but with clinical symptoms.

The other method, with direct determination of thiamine in urin or in blood, perhaps combined with tolerance experiments, ought theoretically to offer greater and surer possibilities of getting an idea of the thiamine conversion and thus giving support to the clinical diagnosis.

The chemical methods of determining thiamine are grouped around two main principles, namely colour-reactions with diazonium salts and thiochrome methods.

Proceeding from the first-mentioned principle, Melnick and Field (1939) have worked out a method of determination for thiamine in urine. They take as their point of departure the reaction described by Prebluda and McCollum with *p*-aminoacetophenone

Further, one can before a quartz-lamp with uviole glass or copper-sulphate cuvette titrate a pure isobutanol solution with thiochrome standard to the same fluorescence as that of the sample and from this calculate the thiamine content (Ritsert 1938, Wang and Harris 1939, Wassmann 1941, Borson 1940 and others). In all cases, however, the result is affected by the fact that the urine itself shows a fluorescence that is not due to the thiamine present. The total fluorescence measured in a sample thus comprises the sum of the thiamine fluorescence and that of the urine itself. The substances that give rise to the last-mentioned fluorescence have not yet been ascertained. (According to Kreuzwendedich von dem Borne 1938, this fluorescence of the urine itself is due to amongst other things the presence of urobilin, urochrome and indoxylacetyl compounds).

The error arising out of the auto-fluorescence can to a certain extent be compensated by the use of suitable filters. The thiochrome fluorescence is pure blue, while the auto-fluorescence in the urine is more blue-green. From various quarters the introduction of blue filters, Euphos filter for filtering off ultra-violet light that has passed the measuring cuvette, or a combination of both has been suggested.

I have investigated the effect on the photometer-reading of various filters by comparing the fluorescence of isobutanol extract that has been decolourized with animal charcoal and taken from unoxidized urine, and thus contains only the substances that condition the auto-fluorescence of the urine, with the fluorescence from pure thiochrome solution. I found in this connection that when reading in filter K VI the intensity of the thiochrome fluorescence was considerably higher in relation to the auto-fluorescence than when reading only in Euphos filter (table I). The figures in the table give the procentual diaphragm opening for the respective samples. In this case, then, there was with Euphos filter light-resemblance in the photometer when the diaphragm opening of the auto-fluorescence sample was maximally opened and the diaphragm of the thiochrome sample was 95 % open. When the Euphos filter was exchanged for K VI, the diaphragm of the thiochrome sample had to be closed down to 60 % in order to obtain light-resemblance. Thus, filter K VI eliminated considerably more of the auto-fluorescences than did Euphos filter.

Table 1.

Urine fluorescence	Thiochrome fluorescence	Filter
100	95	Euphos
100	62	K VI + Euphos
100	60	K VI

An isobutanol extract from untreated urine is read against a pure thiochrome solution in Step-photometer with different filters. The figures represent the percentual diafragm opening (Myrbäck method).

In addition-experiments in urine considerably better readings were obtained when K VI was employed instead of Euphos filter (table 2).

Table 2.

Thiamine added γ per 100 ml	Filter K VI			Euphos filter		
	Total thiamine found γ per 100 ml	Added thiamine recovered γ per 100 ml	Error %	Total thiamine found γ per 100 ml	Added thiamine recovered γ per 100 ml	Error %
0	9.6	0	—	5.3	—	—
2.5	11.5	1.9	—24	8.8	3.5	+10
5.0	14.1	4.5	—10	14.3	9.0	+80
10.0	19.7	10.1	+1	23.0	17.7	+77
20.0	32.2	22.6	+13	28.5	23.2	+16
200.0	231.6	222	+11	210	205	+3
500.0	471	461	—8	480	475	—5
1000	993	983	—2	970	965	—3

A comparison between the results of thiamine determinations in urine with different amounts of thiamine added, when filter K VI and Euphos filter were used (Myrbäck method).

A combination of blue filter and Euphos filter led to such a weakening of the light intensities that reading was as a rule impossible. In photometer determinations, therefore, the use of a blue filter improves the result considerably. In determinations with photo-cell the Euphos filter can presumably not be avoided, on account of the sensitiveness of the photo-cell to ultra-violet light, while in ocular photometer determinations the blue filter alone is preferable. With neither filter, however, was it possible sufficiently to eliminate the unspecific fluorescences.

Table 3.

Urine no.	Thiamine added γ per 100 ml	Urine, not adsorbed		Fuller-earth adsorbed urine	
		Oxid.	Unoxid.	Oxid.	Unoxid.
1	0	66—65	21—31	25—25	18—18
2	0	54—56	22—23	25—	13—12
3	0	61	29	19	11
4	500	613	29	18	11
5	0			25	10
6	500			27	10
7	0	32—30		15	10
8	250	278		18	10

Samples of urine freed from thiamine by adsorption to fuller-earth compared with samples of the same urines which have not been adsorbed. One part of the samples is oxidized and one part is treated as a blank. All the samples have been read in Step-photometer against a 100 γ per — ml thiochrome standard. The figures represent the apparent concentration γ 100 (fluorescence of thiamine plus unspecific fluorescent substances) of thiamine in γ per 100 ml (Myrbäck method).

Further measures had thus to be adopted to compensate the secondary fluorescences. One way of achieving this is to reduce the auto-fluorescence, either by means of preliminary isobutanol extractions of the sample (Ritsert 1938, Pezold and Dittmar 1939, Wang and Harris 1939 and others), whereby the secondary fluorescence but not thiamine is extracted, or by precipitating the thiamine from the sample with wolframate (Myrbäck), or by adsorbing the thiamine of the sample to some active clay, after which the determination is carried out on the adsorbate direct (Hills 1939, Borson 1940) or on a eluate of the same (Hennessy and Cerecedo 1939). These measures, however, only reduce the auto-fluorescence. A considerable auto-fluorescence remains, so that alongside the actual sample one must carry out a blank determination on the urine that represents this remaining auto-fluorescence. By subtracting this value from the fluorescence value of the sample one would obtain the true thiochrome fluorescence.

The blank is produced either by oxidation of a urine sample that has been freed from thiamine by adsorption to fuller-earth (Ritsert 1938, Pezold and Dittmar 1939), or else a blank is employed to which the same reagents have been added as to the actual sample with the exception of potassium ferricyanide (Myrbäck, Wang and Harris 1939, Hennessy and Cerecedo 1939 and others). In

Table 4.

	Urine not adsorbed			Fuller-earth adsorbed urine		
	pH 3	pH 10	Autoclav.	pH 3	pH 10	Autoclav.
Urine Oxidized	18.7	18.4	20.0	9.5	7.3	8.3
No. 1 Unoxidized . .	13.9	13.3	13.7	6.2	5.2	5.3
Urine Oxidized . . .	69.5	58.1	16.5	15.1	14.5	17.0
No. 2 Unoxidized . .	11.3	10.3	9.8	5.6	5.4	6.7

Oxidized and unoxidized samples from urines that have been exposed to pH 3 and pH 10 for 24 hours or have been autoclaved at pH 10 for 2 hours at 123° C. in order to make the urine thiamine-free. The figures represent apparent concentration in γ per 100 ml (Myrbäck method).

the first case one obtains erroneous values owing to the fact that fuller-earth adsorbs not only thiamine but also, though to a lesser extent, the substances that give rise to the auto-fluorescence. The blank thus becomes too low. I have compared the intensity of fluorescence in unoxidized urine samples before and after fuller-adsorption and found a considerable diminution of the fluorescence after the adsorption, which must mean that not only thiamine but also the substances conditioning the auto-fluorescence of the urine have to a certain extent been adsorbed (table 3).

In the other case the blank and the sample are not comparable, as the one is oxidized and the other not. In the literature it is stated that the oxidation can both destroy and increase the auto-fluorescence. In my experiments (table 3), where I have compared the fluorescence in oxidized and unoxidized urine samples that have been freed from thiamine by fuller-adsorption, I have in general found a considerable increase in the fluorescence of the oxidized samples. This increase is probably not due to the fact that thiamine existing in the urine has not been completely adsorbed from the sample, as the fuller-adsorbed samples from one urine and the same urine with addition of thiamine (the urines 3—5) show the same fluorescence values on oxidation.

The same result was obtained in another series of experiments, where I tried to produce a thiamine-free urine, firstly by alkalization of the urine to pH 10 and storing at room-temperature for 24 hours, and secondly by autoclavation at pH 10 for 2 hours at 123°. Surprisingly enough it proved that the thiamine content in the

Table 5.

Thiamine conc. γ/100 ml	Pezold and Dittmar		Myhrbäck		
	Thiamine found	Error %	Thiamine conc. γ/100 ml	Thiamine found	Error %
15	18	+20	5	4 5 5 5 5	+20 0 0 0 0
25	24 27 32	-6 +8 +20	10	11 11 11 11 12	+10 +10 +10
50	49 46 47	-2 -8 -6			+10 +20
200	201 197	+1 -1	20	20	0
500	497 533	-1 +5	25	25 24 25 23 29	0 -6 0 -8
					+16
			50	51 50 52	+ 2 0 +4
			75	76	+ 1
			500	494 474 496 496	- 1 -5 -1 -1

Determinations of thiamine in water-solution with the methods of Pezold and Dittmar (1939) and Myhrbäck.

sample that was kept at room-temperature at pH 10 did not noticeably diminish (table 4).

The problem of compensating in a satisfactory way the auto-fluorescence of the urine has thus not yet been solved. In this connection there is also another difficulty in the thiochrome methods, namely, that in the determination those constituent parts of the urine are present that interfere with and restrict either the formation of thiochrome or the thiochrome fluorescence, as has been pointed out by a number of writers (Marrack and Höllenbergl 1939, Hills 1939, Pyke 1939 and others). Some writers have also recommended addition-experiments for every test to determine the amount of thiamine recovered, to enable one to calculate the real thiamine content.

This disturbing influence of the urine becomes apparent in addition-experiments. I have carried out several such experiments, both with Pezold and Dittmar's method and with a method worked out by Professor Myhrbäck of which he was kind enough to inform me. The latter is intended for measurements with fluorometer; but as I have not had this instrument at my disposal I have instead carried out determinations in Step-photometer against thiochrome standard. In both cases determinations on pure water-solutions have given good results. Table 5.

Table 6.

Thiamine added in γ/100 ml	Exp. 66		Exp. 70		Exp. 80		Exp. 81	
	Thiam- ine found	Recov- ery %	Thiam- ine found	Recov- ery %	Thiam- ine found	Recov- ery	Thiam- ine found	Recov- ery %
0	8.4	—	5.9	—	3.1	—	2.7	—
2.5	11.4	120	8.5	104	6.7	144	—	—
5	12.9	90	10.7	96	5.2	42	6.8	82
10	18.3	99	17.0	111	9.6	65	9.7	70
20	—	—	—	—	16.0	65	17.3	73
200	200	91	216	105	84	41	—	—
400	453	89	436	86	244	48	337	67
1000	989	92	991	99	470	47	527	52

Thiamine determinations with a modification of the method of Myrbäck on urines with different amounts of thiamine added. Read in Step-photometer against a 100 γ % thiochrome standard with filter K VI.

On addition-experiments on urine, on the other hand, Pezold and Dittmar's method gave throughout poor values with losses varying between 6—50 % of the added amount of thiamine. Myrbäck's method, on the other hand, in the modification with Step-photometer used by me, gave in the determination of a number of urines good values, while in a number of others the recovery was poor¹ (table 6).

Summary.

Different modifications of the thiochrome method (Jansen 1936) for the determination of thiamine in urine were tested with particular interest taken in the modifications of Pezold and Dittmar (1939) and Myrbäck.

It was found that the unspecific, non-thiamine fluorescence of the urines could not be completely eliminated with any of the methods tried. Neither filter K VI nor the Euphos filter of the Step-photometer excluded this disturbing fluorescence (tables 1 and 2).

By adsorption to fuller-earth not only the thiamine but also

¹ According to an oral communication with prof. Myrbäck, he has in such cases succeeded in getting recoveries of about 90 per cent by repeated precipitations of the sample with wolframäts.

some of the disturbing substances were adsorbed. The fluorescence of the unoxidized urine (thus without thiochrome-fluorescence) was always somewhat lower if the urine was treated with fuller-earth (table 3).

If the thiochrome was destroyed by autoclavation, the fluorescence was still increased by oxidation (table 4). The oxidation with potassium-ferricyanide not only oxidized the thiamine to thiochrome, but also increased some of the unspecific fluorescence.

With the methods of Pezold and Dittmar and of Myrbäck (with determination in Step-photometer and mercury lamp of Hanau instead of fluorometer) a comparatively good recovery was found in water-solutions of thiamine; but in addition-experiments with urines the results were irregular, and usually gave errors of such magnitude that the methods could scarcely be of any clinical use (table 6).

Literature.

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Über postoperative Gastritis.

(Gastroskopische Untersuchungen)

Von

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Einleitung.

Bereits im Jahre 1926 stellte Schindler unter den Gastriten eine besondere Kategorie auf, die er als *postoperative Gastritis* bezeichnete und worunter er die gastroskopische Veränderungen bei Ulcuspatienten, bei denen Resektion oder Gastroenterostomie ausgeführt worden war, zusammenfasste.

Morphologisch, klinisch und genetisch wird die postoperative Gastritis als besondere Gastritisform aufgefasst, die sich gastroskopisch von den anderen Gastritisformen dadurch unterscheidet, dass die vorhandenen Schleimhautveränderungen nicht gleichartig, sondern im Gegenteil ein Gemisch aller möglichen gastritischen Elemente sind und das, was man sogar in stark angegriffenen, unoperierten Ventrikeln antreffen kann, oft an Intensität übertreffen. Pathologisch-anatomische (Clairmont, Wanke) und gastroskopische Untersuchungen (Henning) haben die Aufstellung dieses neuen morphologischen Begriffs später gerechtfertigt.

Die postoperative Gastritis zeigt nach Schindler ein sehr buntes Bild. Die Schleimhautfalten sind ödematös, geschwollen und tiefrot, oft mit Erosionen besetzt. Zwischen den Falten findet sich oft festsitzender Mucopus. Hypertrophischen Noduli und Exkreszenzen sind eine gewöhnliche Erscheinung, atrophische Elemente dagegen selten. Die Färbung ist oft dunkelrot. Henning unter-

scheidet 3 Formen, die hypertrophische, die katarrhalische und die atrophische Form. Im Gegensatz zu Schindler betrachtet er Erosionen als selten, falls solche aber vorhanden sind, befinden sie sich am Stoma und am anastomierten Darm.

In bezug auf die klinischen Symptome der postoperativen Gastritis erklärt Henning, sie weichen in mancherlei Hinsicht von der Ulcusdyspepsie ab. Sie bestehen aus diffusen Schmerzen im Epigastrium, entweder als Drücken, Aufblähung oder Koliken, die entweder $\frac{1}{2}$ Stunde nach den Mahlzeiten oder unabhängig davon auftreten. Sie haben nicht den Charakter von Hunger, werden durch Essen nicht gelindert und verschlimmern sich bei körperlicher Anstrengung und vornübergebeugter Stellung. Schliesslich können Darmstörungen in Gestalt von Obstipation oder Diarrhoe auftreten.

Die Entstehungsweise dieses schweren Leidens ist noch nicht geklärt. Wanke glaubt, es handle sich dabei um eine Fortsetzung einer bereits vor der Operation bestehenden Gastritis. Es gibt indessen Fälle, wo diese Erklärung nicht anwendbar ist. In einer früheren Arbeit wies der Verf. der gegenwärtigen Arbeit an Hand gastroskopischer Untersuchungen bei 70 v. H. der Patienten mit Ulcus duodeni gastritische Veränderungen nach, die entweder am Corpus allein oder am ganzen Ventrikel lokalisiert waren, während der Ventrikel bei 30 v. H. der Kranken normal war. Es ist somit anzunehmen, dass *Resektion oder Gastroenterostomia bei Ulcus duodeni in der Mehrzahl der Fälle in bereits an Gastritis erkrankten Ventrikeln ausgeführt werden muss*, und in solchen Fällen ist es erklärlich, dass die Gastritis nach der Operation andauert. Andererseits hat man keine sichere Erklärung dafür, dass sich in den Fällen, wo der Ventrikel vor der Operation normal ist, Gastritis entwickelt. Schindler hat die Theorie aufgestellt, der operative Eingriff habe die normale Funktion des Ventrikels verändert durch die Bildung eines Stoma, das eine unphysiologische Wirkungsweise habe, indem es einen unkontrollierbaren Rücktritt von Darmsekret in den Ventrikel gestatte. Schindler stützt diese Annahme auf zwei Beobachtungen, erstens die, dass Gastritis nur in den Fällen auftritt, wo das Stoma die Fähigkeit rhythmischer Kontraktion nicht erlangt und zweitens, dass die postoperative Gastritis (nach Gastroenterostomie) durch Verschluss der Anastomose, angeblich die einzig mögliche Therapie, geheilt werden kann.

Die Auffassungen von der Häufigkeit der postoperativen Gastritis in Europa und Amerika gehen auseinander, und zwar halten Henning und Schindler das Leiden in Europa für ausserordentlich häufig, während es in Amerika (Eusterman & Balfour) für selten gilt. Hierzu ist zu bemerken, dass die letztere Auffassung nicht, wie bei Henning und Schindler, auf gastroskopischen Untersuchungen fusst, sondern auf Folgerungen an Hand klinischer Symptome, von denen gesagt werden darf, dass sie zur Entscheidung der Frage ungeeignet sind, da die Gastritisdiagnose im ganzen genommen eine gastroskopische Diagnose ist. Eusterman & Balfour (Mayo Klinik) glauben, der von ihnen supponierte Unterschied erkläre sich daraus, dass Gastritis in Europa überhaupt häufiger vorkomme als in USA. Es ist jedoch kaum wahrscheinlich, dass diese Annahme einer gastroskopischen Prüfung standhalten würde. Wie dem auch sei, so sind die Probleme bei einem so ernsten Leiden wie die postoperative Gastritis es ist, von grösstem Interesse für einen jeden, der sich vor die Aufgabe gestellt sieht, operierte Ulcuspatienten zu behandeln, was im allgemeinen dem Internisten überlassen wird, für den solche Patienten oft ein »Crux medicorum« sind weil das Leiden unheilbar ist und die Patienten oft zu chronischen Invaliden macht. Aber auch für die Chirurgen ist die Kenntnis der Krankheit von Bedeutung, weil das Ergebnis einer sonst technisch wohl gelungenen Ventrikeloperation dadurch kompromittiert werden kann.

Eigene Untersuchungen.

Angesichts der grossen Bedeutung, die der postoperativen Gastritis beizumessen ist, glaube ich, es dürfte Interesse bieten, meine Beobachtungen über diese Gastritisform, deren Natur ausserhalb des Kreises der Gastroskopiker bisher wenig Beachtung gefunden hat, mitzuteilen. Deshalb sollen im folgenden 9 paradigmatische Krankengeschichten mitgeteilt werden, die jede für sich dazu beitragen dürften, den Charakter des Leidens zu beleuchten. Bei 4 dieser Patienten wurde Gastroenterostomie ausgeführt und bei 5 Resektion. Die Patienten, bei denen es möglich war, wurden längere Zeit hindurch mehrmals gastroskopisch untersucht, wobei sich Gelegenheit bot, das wechselnde Aussehen der Schleimhautveränderungen zu beobachten wie auch ihre Reaktion auf die einge-

schlagene Therapie zu untersuchen. Vor allem ist es die Morphologie, die durch die angeführten Beispiele aufzuhellen getrachtet wird, eine statistische Darlegung der Häufigkeit des Leidens wird nicht angestrebt.

Der Vollständigkeit halber wird ein Fall von Gastroenteroanastome miteinbezogen, wo der Ventrikel 30 Jahre nach der Operation bei zwei mit 2 Jahren Zwischenpause ausgeführten Gastroskopen normal war.

Die Untersuchungen wurden im Kopenhagener Amts (Bezirks)-Krankenhaus zu Gjentofte¹ ausgeführt, deren respektiven Ableitungschefärzten ich hierdurch meinen Dank ausspreche.

I. Fälle von Gastroenterostomie.

No. 1. 45jähriger Mann.

Im Jahre 1923 wurde Gastroenterostomie ausgeführt. Bei der Operation wurden ein fibröses Ulcus duodeni und periduodenale Adhaesionen gefunden.

Danach war der Mann 6 Jahre lang symptomfrei, bekam dann wieder Dyspepsie mit Schmerzen in Cardia und Neigung zum Erbrechen sowie insgesamt 2mal massive Blutung.

Am 16/12 1939 wurde der Kranke mit schwerer Tetania gastrica in die Abt. B des Bezirkskrankenhauses in G. aufgenommen. Blutharnstoff bei der Aufnahme 148 mg %, Serumchlor 310 mg %. Vorübergehend Albuminurie. Nüchternsekret 400 cm³. *Gastroskopie*: Die Anastomose befindet sich distal an der Rückwand und ist ohne Peristaltik. Der Ventrikel ist im ganzen genommen Sitz einer schweren Gastritis mit Rötung, Oedem und Succulenz. Die Falten sind geschwollen, granuliert, mit zahlreichen erosiven Elementen.

Epikrise: Ein 45jähriger Mann, bei dem im Alter von 29 Jahren wegen eines fibrösen Ulcus duodeni Gastroenterostomie ausgeführt worden war, bekam nach einer 6jährigen symptomfreien Periode schwere Dyspepsie und massive Blutungen, die mit Tetania gastrica und schwerer Atonie kulminierten. Als Ursache der Symptome wurde gemischte Gastritis superfizieller, hypertrophischer und erosiver Natur ermittelt.

No. 2. 65jährige Frau.

Operation 1911: Gastroenterostomia retrocolica post. und Enterostomie. Am Pylorus wurde eine sternförmige Narbe gefunden, die sich nicht durch den Pylorus einstülpfen liess.

¹ K.A.S.G.

Sie ist nie zu irgendeinem Zeitpunkt symptomfrei gewesen. Hält ständig Diät.

1938 wegen Anaemia Faberi in die Abt. aufgenommen.

Probemahlzeit: Achylie.

Röntgen: Der Ventrikel entleert sich durch die Anastomose. Pylorus geschlossen. Entsprechend der Curv. minor nahe dem Pylorus ist eine unregelmässige Prominenz, möglicherweise ein Ulcus, zu sehen.

Gastroskopie I (4/3, 1938): Ausgeprägte Gastritis im ganzen Ventrikel mit Rötung, Oedem und Succulenz. Pylorus verschoben, kann nicht ins Gesichtsfeld gebracht werden. Weder Erosionen noch Ulcera. Distal an der Rückwand ist ein Stoma mit ausgeprägt entzündlichen Veränderungen und ohne Peristaltik zu sehen.

Mit Ulcuskur behandelt und gebessert entlassen.

11/5, 1938 Wiederaufnahme wegen Verschlimmerung der Symptome.

Röntgen: Keine Ulcera, aber Zeichen von Gastritis.

Gastroskopie II (18/5, 1938): Die Veränderungen sind viel erheblicher als das letzte Mal. Überall sind heftige Rötung, Oedem und Succulenz sowie festsitzender Schleim zu sehen, besonders ausgeprägt um den Angulus. Stoma wie zuvor. Längs der Curv. min. mehrere kleine submuköse Blutungen, aber weder Erosionen noch Ulcera oder hypertrophische Elemente.

Wieder mit Ulcuskur behandelt und gebessert entlassen.

14/9, 1938 Wiederaufnahme wegen erneuten Aufflackerns der Symptome.

Gastroskopie III (19/8, 1938): Die gastritischen Veränderungen sind noch ausgeprägter als das letztmal und nehmen distal im Ventrikel an Intensität zu. Pylorus ist diesmal zu sehen; er ist ohne Peristaltik. Stoma unverändert. Keine hypertrophischen Elemente, Erosionen oder Ulcera. Die Kranke wird wiederum mit Ulcuskur behandelt, bekommt jetzt aber ausserdem tägliche Ventrikelspülungen, womit sie zuhause fortfährt.

Nachuntersuchung 26/4, 1939: Nachdem sie sich zuhause täglich ausgespült hat, sind keine nennenswerten Symptome mehr vorhanden.

Gastroskopie IV: Intensive Rötung und Succulenz. Die Veränderungen wie das letztmal, jedoch ist die Gastritis um das Stoma etwas stärker und breitet sich im Jejunum sichtlich aus. Weder Erosionen, Ulcera noch hypertrophische Elemente.

Epikrise: 65jährige Frau, die als 38jährige wegen eines ausgeheilten Ulcus ad Pylorum einer Gastroenterostomie unterzogen worden und seither nie symptomfrei gewesen ist.

27 Jahre nach der Operation wird eine Pangastritis ermittelt, die im Laufe eines Jahres 3mal mit Ulcuskur behandelt wird; die Wirkung ist aber nur vorübergehend. Subjektive Besserung tritt erst ein, als die Kranke lernt, den Magen täglich auszuspülen.

Insgesamt werden 4 Gastroskopien ausgeführt, die alle ausge-

prägte superfizielle Gastritis aufdecken, die sich allmählich verschlimmert. Bei der letzten Untersuchung, 1 Jahr nach der ersten, berichtet die Kranke, die Dyspepsie sei jetzt geringfügig. Trotzdem ergibt die Gastroskopie kein Zeichen von Besserung, sondern im Gegenteil eine Verschlimmerung.

No. 3. 69jähriger Mann.

1918 wegen *Ulcus perforatus* operiert. 1922 wurde Gastroenterostomia retrocolica post. ausgeführt.

1935 wegen leichter Dyspepsie in die Abt. B des K. A. S. G. aufgenommen und mit Ulcuskur behandelt.

Röntgen: Der Ventrikel entleert sich durch die Anastomose. Keine Ulcera.

Wiederaufnahme 1939 wegen kurzfristiger Melaena, die aber bereits aufgehört hatte.

Gastroskopie (28/2, 1939): Im Fundus ist eine fleckförmige Atrophie zu sehen. Der übrige Teil des Ventrikels weist leichte diffuse Rötung namentlich rings um das Stoma auf, das Peristaltik zeigt. Keine Erosionen der Ulcera.

Epikrise: 69jähriger Mann, der als 48jähriger wegen perforiertes *Ulcus* operiert worden ist und bei dem im Alter von 52 Jahren Gastroenterostomie ausgeführt wird. 13 Jahre nach der Operation wird er wegen leichter Dyspepsie ins Krankenhaus aufgenommen und 17 Jahre danach wegen kurzfristiger Melaena. Im Stoma wird Peristaltik nachgewiesen, im Ventrikel geringfügige Gastritis atrophicans.

No. 4. 62jähriger Mann.

1908 wegen »Gastritis« behandelt. Da die Ausleerung verzögert war, wurden Gastroenterostomie und Enteroanastomose ausgeführt. Seither hat er keine eigentlichen Ventrikelsymptome gehabt und keinerlei Diät gehalten.

1938 wegen Anorexia und Achylia in die Abt. B des K.A.S.G. aufgenommen.

Röntgen: Bulbus deform. Das Kontrastmittel geht durch Anastomose und Pylorus.

Gastroskopie I (4/11, 1938): Hinter dem Angulus ist ein kurzer Kanal zu sehen, der in einem Pylorus ohne Peristaltik endigt. Die Schleimhaut ist überall normal ohne Zeichen von Gastritis. Es gelingt nicht, die Anastomose zu finden.

Der Kranke wird gebessert entlassen, 1940 aber wiederaufgenommen, weil er an Gewicht verloren hat. Keine Dyspepsie.

Gastroskopie II (27/3, 1940): Die Anastomose ist jetzt aufwärts an der Rückwand zu sehen. Sie ist etwas rau, wie die meisten Stomata,

aber ohne Entzündungsreaktionen. Man sieht einzelne rhythmische Kontraktionen. Wie Schleimhaut ist, ebenso wie letzt, überall normal, insbesondere sind keine atrophischen Elemente zu sehen.

Epikrise: 67jähriger Mann, bei dem im Alter von 37 Jahren Gastroenterostomie ausgeführt wurde wegen »Gastritis« mit Retention. 30 Jahre später wird er wegen Appetitlosigkeit aufgenommen, hat aber keine Dyspepsie. Es wird Achylie nachgewiesen. Die Ventrikelschleimhaut ist normal. Nach 2 Jahren wird die Gastroskopie wiederholt. Der Ventrikel ist ständig normal und das Stoma zeigt Peristaltik.

No. 5. 26jähriger Mann.

1935 wegen eines perforierten Ulcus duodeni operiert. Das Ulcus wurde suturiert und es wurde Gastroenterostomie ausgeführt.

30/12, 1940 wegen eines perforierten Ulcus ventriculi in die Abt. A des Bispebjerg Hospital aufgenommen. Bei der Operation wurde eine erbsengrosse Perforation an der Vorderseite des Ventrikels nahe dem Pylorus gefunden. Das Ulcus wird suturiert. Es wird erfolglos nach der früher ausgeführten Anastomose gefahndet. Auch die nachherige Röntgenuntersuchung deckt keine Anastomose auf.

Gastroskopie (19/2, 1941): Abwärts nach dem Angulus hin sind leichtere hypertrophische Veränderungen zu sehen, denn die Schleimhaut hat hier ein granuliertes Aussehen. Proximal dem Angulus ist eine sternförmige Narbe in der Schleimhaut zu sehen. An der Rückwand dicht neben der Curv. minor wird eine zweite sternförmige Narbe, möglicherweise Überreste der Anastomose, gefunden.

(Der Fall wurde von Dr. med. Ottsen im Jahre 1941 in Ugeskrift for Læger veröffentlicht).

Epikrise: 26jähriger Mann wurde im Alter von 21 Jahren wegen eines perforierten Ulcus duodeni operiert, wobei gleichzeitig Gastroenterostomie ausgeführt wurde. 5 Jahre später wurde er nochmals operiert, und zwar wegen eines perforierten Ulcus ventriculi. Die früher angelegte Anastomose ist weder bei der Operation noch später bei der Röntgenuntersuchung nachweisbar.

Die Gastroskopie deckt eine leichtere, örtlich hypertrophische Gastritis und zwei Narben auf.

II. Fälle von Resektion.

No. 6. 42jährige Frau.

1928 wegen Ulcus operiert, mit Resektion. Sie wurde nicht symptomfrei. 1933 erfolglose medizinische Behandlung. Invalidenrente zuerkannt.

mittelt, dagegen ist eine Resektion nicht nachweisbar. Während der obere Magenabschnitt verhältnismässig normal ist, wird im unteren Abschnitt eine heftige, gemischte Gastritis mit erosiven Elementen nachgewiesen, die sich bei Ulcuskur und Ventrikelspülungen bessert. Es wird abermals eine Resektion ausgeführt. Nach 1 Jahr wird im oberen Teil des Magens Atrophie nachgewiesen, während abwärts, besonders rings um die Anastomose, ebensolche Veränderungen ermittelt werden wie früher, die sich bis in den Darm fortsetzen.

No. 7. 35jähriger Mann.

1932 wegen Ulcus perforat. operiert, mit Übernähung. Einige Monate später wurde Resektion ausgeführt. Kurz darauf wiederum Ventrikelsymptome.

1936 in die Abt. B. des K. A. S. G. aufgenommen. Problemahlzeit: 33 cm³ 40/60.

Röntgen: Ulcus pepticum jejuni. Behandlung: Ulcuskur mit vorübergehender Besserung.

1937 Wiederaufnahme wegen heftiger Symptome und Erbrechen.

Röntgen: Verwischtes Relief. Canalis und Pylorus fehlen. Ebenso wie bei der früheren Untersuchung ist ein verdächtiger, aber nicht ganz konstanter Fleck nahe dem Stoma zu sehen.

Gastroskopie I (1937): Der Ventrikel ist ganz kurz, überall Sitz schwerer Gastritis. Die Schleimhaut ist hochrot, samtartig, oedematös. Die Veränderungen sind rings um das Stoma und bis in den Darm, wo sich zahlreiche frische Erosionen befinden, besonders ausgeprägt. Keine Peristaltik hier. Eben proximal vom Stoma ist eine 1 cm³ grosse Ulceration älteren Datums zu sehen.

Es wird mit Ulcuskur und täglichen Ventrikelspülungen mit Salzwasser behandelt, womit er nach der Entlassung fortfährt.

Nachuntersuchung 1938: Er spült den Ventrikel täglich, hält Schon-diät, hat aber immer noch etwas Dyspepsie. Kein Erbrechen.

Gastroskopie II: Die entzündlichen Veränderungen sind beträchtlich zurückgegangen, sie sind immer noch am stärksten rings um das Stoma und erstrecken sich in den Darm. Weder Erosionen noch Ulcera.

Spätere Auskunft: Der Kranke verstarb 1939 nach Reoperation in einem anderen Hospital.

Epikrise: 35jähriger Mann, der im Alter von 30 Jahren innerhalb eines Jahres zuerst wegen eines perforierten Ulcus operiert und danach einer Resektion unterworfen wurde. Er ist nie zu irgendeiner Zeit symptomfrei gewesen. Ulcuskur 4 Jahre nach der Operation bewirkt nur vorübergehende Besserung. 5 Jahre nach der Operation wird schwere, sich bis in den Darm erstreckende

Gastritis von gemischtem Typus und ein grosses, älteres Ulcus nachgewiesen. Es wird wieder Ulcuskur angewandt und ausserdem tägliche Ventrikelspülungen, womit der Kranke zuhause fortfährt. Der Zustand ist leidlich.

Nach ein Jahrlang fortgesetzten Spülungen wird deutliche Besserung der Gastritis nachgewiesen, die jedoch ständig denselben Typus zeigt, obwohl ohne Erosionen. Die Wunde wird nicht ermittelt. Nach 1 Jahr stirbt er im Anschluss an nochmalige Resektion.

No. 8. 41jährige Frau.

1937 wird auf den Verdacht auf Cancer Ventrikelresektion ausgeführt. Es wurde weder Cancer noch Ulcus gefunden, die Mikroskopie des Präparates deckte aber Gastritis auf.

1939 wird die Kranke in die Abt. B des K. A. S. G. wegen uncharakteristischer Dyspepsie aufgenommen.

Röntgen: Resektionsventrikel.

Gastroskopie: Das Stoma liegt gerade vorn und hat Peristaltik. Die Schleimhaut ist überall, aber namentlich aufwärts im Corpus, Sitz leichter Gastritis mit leichter Rötung und Succulenz. Die Vorderwand weist Zeichen von leichterer hypertrophischer Gastritis auf. Weder Ulcera noch Erosionen. Behandlung mit Ulcuskur bewirkt subjektive Besserung.

Epikrise: Bei einer 41jährigen Frau wird auf den Verdacht auf Cancer Resektion ausgeführt. Die Operation deckt Gastritis auf. Nach 2 Jahren wird aufwärts im Ventrikel leichtere gemischte Gastritis ermittelt. Das Stoma weist Peristaltik auf.

No. 9. 49jähriger Mann.

1931 wird wegen Ulcus Resektion ausgeführt. Seither ausgeprägte tardive Dyspepsie ohne Linderung durch Essen.

1937 Aufnahme in die Abt. B des K. A. S. G.

Röntgen: Nischenartige Erscheinung am Stoma.

Behandlung mit Ulcuskur von kurzfristiger Wirkung.

1939 Wiederaufnahme wegen Melaena von kurzer Dauer. Blutharnstoff bereits bei der Aufnahme normal.

Röntgen: Wie zuvor.

Gastroskopi I (31/9, 1939): Der Ventrikel ist kurz. Die Schleimhaut ist Sitz mässiger Rötung und Succulenz mit einzelnen hypertrophischen Elementen längs der Curv. maj. und an der Vorderwand. Das Stoma ist rau, Sitz von Gastritis, ohne Peristaltik. Eben proximal davon wird an der Curv. min. eine 1 cm lange, lineare, frische, in Heilung begriffene Ulceration ermittelt.

Behandlung mit Ulcuskur bewirkte subjektive Besserung.

Gastroskopie II (26/10, 1939): Die Gastritis hat sich besonders um das Stoma verschlimmert.

Trotz den geringen subjektiven Symptomen werden alsbald auf Grund der gastroskopischen Befunde Ulcuskur und Ventrikelspülungen verordnet.

Gastroskopie III (23/11, 1939, nach der Kur): Die gastritischen Veränderungen sind etwas zurückgegangen, besonders abwärts um das Stoma, denn die Rötung ist weniger intensiv, das Oedem und die Succulenz haben abgenommen, die hypertrophischen Partien sind dagegen unverändert.

14/12 1939 wurde der Kranke wegen Abdominalia acuta in die Abt. D des K. A. S. G. aufgenommen. Es handelte sich um drohende Perforation mit Gastrektasie. Die Operation deckte einen kleinapfelgrossen Ulcustumor unten im Duodenum auf.

Epikrise: Bei einem 49jährigen Manne war im Alter von 41 Jahren wegen Ulcus Resektion ausgeführt worden. Seither hat er leichtere Dyspepsie gehabt. 6 Jahre nach der Operation Behandlung mit Ulcuskur von kurzfristiger Wirkung. 8 Jahre nach der Operation Melaena von kurzer Dauer. Es wurden leichtere gemischte Gastritis und ein in Heilung begriffenes frisches Ulcus ermittelt. Subjektiv erfolgte Besserung, die Gastroskopie deckte aber eine Verschlimmerung auf, weshalb erneute Kur und Ventrikelspülungen verordnet wurden. Nach 1 Monat wird Besserung der Gastritis wahrgenommen, aber bereits 1 Monat später wird der Kranke mit akuten Ventrikelsymptomen in die chirurgische Abteilung aufgenommen, wo ein grosser Ulcustumor im Duodenum nachgewiesen wird.

No. 10. 33jähriger Mann.

1938 Resektion wegen Ulcus duodeni. Nach ein paar Monaten wiederum Ventrikelsymptome mit Erbrechen.

Röntgen: Grobe Falten. Normale Passage durch die Anastomose. Dicht neben dieser ein kleiner Fleck, der in den Ventrikel vorragt.

Gastroskopie I (8/2, 1939): Es ist eine leichte superficielle Gastritis im Corpus zu sehen. Distal zur Vorderwand sind 2 feuerrote, erbsengrosse Hervorragungen zu sehen, die das Aussehen einer »embolischen Herd gastritis« haben. Weder Erosionen noch Ulcera.

Im Mai 1939 Wiederaufnahme in die Abt. D des K. A. S. G., weil die Symptome sich noch verschlimmert haben.

Röntgen: Ulcus auf der Curv. min.

Nochmalige Resektion. Kein Ulcus, aber in der Schleimhaut wurde eine Sutura gefunden, durch die dieselbe abgeschürft worden war.

Da die Symptome danach nicht abklagen, wurde er im April 1940 wiederaufgenommen.

Gastroskopie II (23/4, 1940): Die Resektionsstelle findet sich abwärts und gleicht, abgesehen davon, dass der Rand etwas zackig ist, einem normalen Pylorus mit Peristaltik. Proximal davon findet sich auf der Curv. min. eine frische, knapp erbsengrosse Erosion. Der ganze Ventrikel ist übrigens Sitz einer leichteren superficiellen Gastritis mit Rötung und Succulenz.

Die Probemahlzeit ergab Achylie.

Eine Ulcuskur bewirkte etwas Besserung.

Gastroskopie III (9/6, 1940): Die Erosion ist verschwunden, aber die Gastritis ist unverändert.

Nachuntersuchung im August 1940: Die Ventrikelanfälle sind rezidiert. Pat. hat wieder ausgeprägte tardive Dyspepsie mit Linderung durch Erbrechen. Hält strenge Diät. Kein Zeichen von Avitaminose.

Gastroskopie IV (16/8, 1940): Die Gastritis hat sich verschlimmert. Überall sind intensive dunkle Rötung, starke Succulenz und Oedem der dicken, gewundenen Falten zu sehen. Die Veränderungen sind rings um das Stoma am ausgeprägtesten und erstrecken sich in den Darm. Weder Ulcera noch Erosionen. Es wird 30 g Mucin in 1 Liter Milch, auf 6 Mahlzeiten verteilt, verordnet.

Nachuntersuchung im Sept. 1940: Die Symptome sind unverändert. Der Mann ist arbeitsunfähig.

Gastroskopie V (4/9, 1940): Die Gastritis hat sich noch mehr verschlimmert. Der ganze Ventrikel und der angrenzende Darm sind flammendrot mit festsitzenden Schleimfladen. Keine atrophischen oder erosiven Elemente.

Es werden tägliche Ventrikelspülungen mit Salzwasser verordnet.

Nachuntersuchung im Januar 1941: Die Symptome sind völlig unverändert. Er hat heftige Schmerzen bis in den Rücken. Arbeitsunfähig.

Gastroskopie VI (28/1, 1941): Die Falten sind jetzt deutlich granuliert. Rötung, Succulenz und Schleimbelag unverändert.

Epikrise: Bei einem 33jährigen Manne wurde wegen Ulcus duodeni vor Jahresfrist eine Resektion ausgeführt, ohne die Symptome zu bessern. Jetzt leidet er an leichter superfiizieller Gastritis mit »embolischer Herdgastritis«. Nach 3 Monaten deckt die Röntgenuntersuchung ein »Ulcus« auf, weshalb nochmals zur Resektion geschritten wird. Als Erklärung des Röntgenbefundes wird in der Schleimhaut eine Sutura ermittelt, die die Schleimhaut abgeschürft hat. Dem entspricht der gastroskopische Befund, der als »Herdgastritis« gedeutet wird. Ein knappes Jahr danach wird der Kranke wegen Ventrikelsymptomen wieder aufgenommen. Es wird Achylie nachgewiesen und die Gastritis ist unverändert, dagegen wird jetzt eine frische Ulceration gefunden, die nach Ulcuskur abheilt, während die Gastritis unverändert bleibt. 2 Monate später

sind die Symptome rezidiert und die Gastritis hat sich sehr verschlimmert. Trotz der Behandlung, zuerst mit Mucin und danach mit Ventrikelspülungen, halten sich die Symptome und wiederholte Gastroskopien zeigen allmähliches Fortschreiten der Gastritis, worin im Laufe etwa eines halben Jahres hypertrophische Elemente erscheinen.

Diskussion.

Die Durchsicht der vorstehenden Krankengeschichten ergibt, dass die gewählten Beispiele sich ergänzen und zusammen einen Begriff liefern von der Mannigfaltigkeit der Äusserungsformen der postoperativen Gastritis.

Nur einer der 10 Patienten hatte normale Ventrikelschleimhaut und dementsprechend keine eigentliche Dyspepsie (No. 4). Der Fall ist insofern interessant, als seit der Ausführung der Gastroenterostomie bis zu dem Zeitpunkte der ersten gastroskopischen Untersuchung 30 Jahre verstrichen waren, ohne dass sich postoperative Gastritis eingestellt hätte. Die Operation war wegen »Gastritis« mit verzögerter Entleerung ausgeführt worden. Die Diagnose war damals an Hand der Symptome gestellt worden. Nach 30 Jahren ergab die Röntgenuntersuchung Zeichen eines ausgeheilten Ulcus duodeni ohne Pylorostenose und mit Entleerung durch den Pylorus wie auch durch die Anastomose, während die Probemahlzeit Achylie aufdeckte. Es ist möglich, dass die Entstehung einer postoperativen Gastritis durch das Zusammentreffen dieser Verhältnisse verhindert worden ist.

Bei all den übrigen 9 Patienten war der Ventrikel Sitz mehr oder weniger ausgeprägter Entzündungsveränderungen, die meistens von bunter Polymorphie waren. Vergleicht man die gastroskopischen Befunde bei Gastroenterostomie und Resektion miteinander, so ergibt sich, dass die nämlich Veränderungen gleicher Art sind. Nur in 2 Fällen lässt sich die Gastritis in dem gewöhnlichen Gastritisschema rubrizieren, nämlich bei Pat. No. 2, die eine reine, wenn gleich sehr schwere Gastritis superficialis hatte, und Pat. No. 3, der an reiner Gastritis atrophicans litt. Bei all den übrigen Patienten deckte die Untersuchung ein Gemisch von superfiziellen, hypertrophischen, atrophischen, erosiven und ulcerösen Elementen auf. Nach allem zu urteilen scheint es jedoch, als ob die superfizielle Gastritis das Grundelement der postoperativen Gastri-

tis bildet, denn sie ist anscheinend der Ausgangspunkt all der anderen Veränderungen und der Boden, aus dem diese Veränderungen erwachsen. Das Auftreten der verschiedenen Elemente scheint an keine bestimmten Regeln gebunden zu sein. Es ist beispielsweise gelungen, einerseits einen Übergang von superficiell-hypertrophisch-erosiver zu atrophischer Gastritis festzustellen (No. 6) und andererseits die Entwicklung hypertrophischer Elemente in superficieller Gastritis zu beobachten (No. 10), was als Eigentümlichkeit der postoperativen Gastritis zu bezeichnen ist. Unter den auftretenden Elementen sind Erosionen und Ulcerationen die flüchtigsten. Sie verschwinden ebenso rasch wie sie gekommen sind, was jedoch nicht als für die postoperative Gastritis eigentümliches Phänomen anzusprechen ist.

Morphologisch interessant ist der Fall No. 6: in einem bilocularen Ventrikel war das Aussehen der beiden Ventrikelabschnitte sehr verschieden, denn im distalen Abschnitt wurde heftige Gastritis ermittelt, während der proximale fast normal war. Nach der zweiten Resektion, auf die Achylie folgte, entwickelte sich im oberen Teil im Laufe eines Jahres Atrophie und abwärts besserte die Gastritis sich nicht nur nicht, sondern verschlimmerte sich im Gegenteil und zeigte Neigung, sich in den Darm hinein zu erstrecken. Der Fall ist als gastroskopische Seltenheit zu betrachten und die Genese völlig unklar.

Bei 4 Patienten (No. 1, 2, 7, 9), die alle Gastritis hatten, waren im Stoma keine Kontraktionen nachweisbar. Bei 4 anderen (No. 3, 4, 8, 10) war im Stoma zwar Peristaltik zu sehen, dennoch aber wurden bei 3 derselben (No. 3, 8, 10) sehr ausgeprägte Entzündungsveränderungen ermittelt. Diese Beobachtung zeigt m. a. W., dass die postoperative Gastritis nicht ausschliesslich in den Fällen entsteht, wo das Stoma die Fähigkeit der Kontraktion nicht erlangt. Dies Verhalten kann sonach für die Pathogenese der Gastritis keine entscheidende Rolle spielen.

Ein lehrreicher Irrtum lag bei einem Patienten (No. 10) vor, bei dem röntgenologisch nach der ersten Resektion neben dem Stoma eine kleine Hervorragung in den Ventrikel — also das Gegenteil von einer Nische — nachgewiesen wurde. Dementsprechend deckte die Gastroskopie ein Bild auf, das Ähnlichkeit mit einer sogenannten »embolischen Herdgastritis« hatte. Bei der zweiten Resektion, die auf Grundlage der Röntgendiagnose: pep-

tisches Ulcus ausgeführt wurde, wurde indessen eine Suture ermittelt, die die Schleimhaut erodiert hatte. Demnach handelte es sich nicht um embolische »Herdgastritis«, sondern um eine Fremdkörpergastritis. Eine gastroskopische Differentialdiagnose zwischen diesen beiden Prozessen ist, wenn die Suture selbst nicht sichtbar ist, allerdings kaum möglich und insofern auch belanglos, als beide Leiden eine günstige Prognose haben und im allgemeinen keine Indikation für Operation liefern.

Die Bedeutung, die Schindler dem Verschluss der Anastomose für die Heilung der postoperativen Gastritis beimisst, wird durch diese Untersuchungsreihe nicht erhörtet. In einem Falle (No. 5) lag zwar spontaner Verschluss einer Gastroenterostomie vor, über den Zustand des Ventrikels vor dem Verschluss ist aber nichts bekannt, weil der Kranke früher nie gastroskopiert worden war. Dennoch verdient es vielleicht Beachtung, dass die nachgewiesenen gastroskopischen Veränderungen von geringer Intensität wie auch wenig ausgebreitet waren, und dass die Schleimhaut zum grössten Teil normal war.

Die Neigung der postoperativen Gastritis, das Stoma und den anastomierten Darm in besonders hohem Grade anzugreifen, ist aus den Beispielen deutlich ersichtlich, und es kann ausserdem festgestellt werden, dass diese Neigung von der Kontraktionsfähigkeit des Stoma unabhängig ist. Noch ein weiterer Umstand wird durch die Untersuchungen erläutert. Bekanntlich ist diskutiert worden, ob es denkbar sei, dass die Salzsäure an den im Ventrikel und Darm beobachteten Operationsfolgen, die vielfach als peptisch aufgefasst werden, schuld sein könne. Die hier beschriebenen Fälle zeigen indessen, dass das Vorhandensein freier Salzsäure nicht Voraussetzung für die Entstehung postoperativer Gastritis ist, denn in den Fällen mit der ausgeprägtesten Gastritis (No. 2, 6, 10) lag Achylie vor und in 2 Fällen verschlimmerte sich die Gastritis sogar gleichzeitig mit oder nach dem Beginn der Achylie. Die Achylie ist offenbar eine Folge der Gastritis und ein Ausdruck dafür, dass dieselbe eine gewisse Intensität erreicht hat.

In bezug auf die beobachteten klinischen Symptome sei bemerkt, dass sie der von Henning angegebenen Dyspepsie sehr gut entsprechen.

Die Ergebnisse der angewandten Therapie sind nicht ermutigend. Dass wiederholte Resektion das Fortschreiten der Gastritis

nicht zu hindern vermag, erhellt aus 2 Beispielen (No. 6 und 10), und eine wirksame medizinische Therapie lässt sich nach den bisherigen Erfahrungen nicht angeben, wenngleich es der Mühe wert zu sein scheint, Ulcuskur mit Ventrikelspülungen zu kombinieren. In ein paar Fällen (No. 6 und 7) wurde danach subjektive wie auch objektive Besserung nachgewiesen. Bei der Bewertung der therapeutischen Ergebnisse darf man sich indessen von einer subjektiven Besserung nicht täuschen lassen, denn solche ist nicht immer gleichbedeutend mit einer Besserung der Gastritis. So enthält das gegenwärtige Material ein Beispiel dafür, dass eine Besserung der Symptome sehr wohl mit einer Verschlimmerung der Gastritis einhergehen kann (No. 2), und der miteinbezogene Fall No. 10 zeigt, dass sogar eine, lange Zeit hindurch angewandte Therapie mit Ulcuskur, Ventrikelspülungen und Mucin weder imstande ist, die Gastritis zum Aufhören zu bringen noch die Entwicklung der bösartigsten, d. h. der hypertrophischen Gastritis-elemente zu hindern. Im grossen ganzen ist zu betonen, dass in den Fällen mit nachweisbarer objektiver Besserung lediglich die flüchtigen Veränderungen, die Erosionen und Ulcerationen schwinden, während das Grundelement, die Gastritis, der medizinischen Behandlung gegenüber ausserordentlich resistent ist (No. 6, 7, 9); insbesondere ist damit zu rechnen, dass die hypertrophischen und atrophischen Elemente, wenn sie einmal vorhanden sind, sich schwerlich von irgendeiner Therapie beeinflussen lassen.

Wie aus den angeführten Beispielen erhellt, ist die postoperative Gastritis als eines der ernstesten Ventrikelleiden zu betrachten, welches in morphologischer wie auch prognostischer Hinsicht eine Sonderstellung unter den Gastriten einnimmt.

Konklusionen.

1. Die in Operationsventrikeln auftretende Gastritis ist im allgemeinen durch ausgeprägte Polymorphie charakterisiert, da sie aus superfiziellen, hypertrophischen, erosiven, atrophischen und eventuell ulcerösen Elementen zusammengesetzt ist, weshalb es statthaft ist, sie als besondere Gastritisform zu betrachten.

2. Die Gastritis entwickelt sich unabhängig davon, ob freie Salzsäure vorhanden ist und ob das Stoma die Fähigkeit rhythmischer Kontraktion erlangt.

3. Eine etwaige objektive Besserung betrifft lediglich die erosiven und ulcerösen Elemente, während die atrophischen und hypertrophischen Veränderungen wahrscheinlich unheilbar sind.
4. Eine wirksame Therapie lässt sich nicht angeben. Am erfolgreichsten ist möglicherweise die Kombination von Ulcuskur und Ventrikelspülungen, subjektive und objektive Besserung brauchen aber nicht miteinander einherzugehen und der Besserung der Symptome zum Trotz kann die Gastritis fortschreiten.

Zusammenfassung.

Zur Beleuchtung der Morphologie der postoperativen Gastritis werden 10 Krankengeschichten von Patienten mitgeteilt, bei denen Resektion und Gastroenterostomie ausgeführt worden und die auch gastroskopisch untersucht worden sind. Nur in 1 Falle war der Ventrikel normal. Bei den übrigen 9 Patienten wurden ausgeprägte gastritische Veränderungen nachgewiesen. In der Mehrzahl der Fälle bestanden die Veränderungen aus einem Gemisch von superficialen, hypertrophischen, atrophischen, erosiven oder ulcerösen Elementen, die vorzugsweise am Stoma und am anastomierten Darm lokalisiert waren. Es wird festgestellt, dass die postoperative Gastritis auch, wenn das Stoma die Fähigkeit rhythmischer Kontraktion erlangt, entstehen kann, und dass sie das Vorhandensein freier Salzsäure nicht zur Voraussetzung hat.

Morphologisch ist die postoperative Gastritis als besondere Gastritisform aufzufassen.

Im Falle objektiver Besserung umfasste dieselbe nur die superficialen, erosiven und ulcerösen Elemente, die hypertrophischen und atrophischen Elemente sind dagegen als unheilbar zu betrachten.

Eine wirksame Therapie kann nicht angegeben werden. Erneute Resektion hindert das Fortschreiten der Gastritis nicht. In gewissen Fällen erfolgte nach kombinierter Ulcuskur und Ventrikelspülungen subjektive und objektive Besserung, die Mucinbehandlung schien dagegen wirkungslos zu sein. Besserung der klinischen Symptome braucht nicht von Besserung der Gastritis begleitet zu sein, sondern kann im Gegenteil mit einer Verschlimmerung derselben einhergehen. Die Prognose des Leidens ist als ernst zu betrachten.

Summary.

In order to elucidate the question of the morphology of the postoperative gastritis 10 patients, on which resection or gastroenterostomy was performed, were examined gastroscopically. In one case only the stomach was found normal. In all the other 9 cases pronounced gastritic changes were demonstrable, which in the major part consisted of a mixture of superficial, hypertrophic, atrophic, erosive or ulcerative elements, mostly localized to the stoma and the anastomosing intestine. It is established that the postoperative gastritis may develop even if the stoma shows rhythmic contractions or free hydrochloric acid is lacking. Morphologically the postoperative gastritis proves to be a special form of gastritis.

In cases where objective improvement was observed, only the superficial, erosive or ulcerative elements were concerned, while the hypertrophic and atrophic elements seem to be incurable. No effective therapy can be indicated. Repeated resection does not stop the development of the gastritis. In some cases improvement was observed after a combination of Sippy treatment and stomach lavages, while Mucin seems to be ineffective.

Clinical improvement does not mean improvement of the gastritis, on the contrary it may be accompanied by aggravation of the latter. The prognosis must be considered bad.

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A Case of Myelomatosis with Diffuse Plasma Cell Infiltration of Lymph Nodes, Liver, Spleen, Kidneys, and Lungs.

By

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(Submitted for publication July 26, 1943).

The case reported below was deemed of interest by its elucidation of the relation of myelomatosis to the other malignant diseases of the myelopoietic system.

History:

No. 105/1942. Male, aged 62. The father is said to have died from tuberculosis, otherwise there is no record of the patient having lived in a tuberculous environment.

The symptoms set in 5 months prior to admission with cough and expectoration of whitish lumps. Gradually fatigue developed with functional dyspnea and general debility. Beyond this no symptoms, particularly no pain anywhere.

Up to 12 years before admission the patient had in the main been in good health. He then developed pneumonia from which he was considered to have completely recovered. 7 years later, that is, 5 years before the onset of the present malady, he was admitted to Præsto District Hospital at Næstved for an affection of the lungs which began with coughing, a stitch in the chest, and a temperature of about 39° C. The patient was admitted 5 days after the onset, and stethoscopy showed symptoms of a leftsided pneumonia and dry pleuritis. Tp. 39.6, pulse 120.

Roentgenograms of the lungs few days after admission showed small spots of infiltration in the upper half of the left lung, extending down into the lower lobe. A little above the middle of the lung was seen a cavity the size of a green walnut half filled with fluid. One month later the same

picture was observed, though the supposed cavity was no longer so distinct.

The sputum was examined repeatedly for T. B. with a negative result, just as the examination of the stomach wash by the State Serum Institute showed no T. B. The temperature was mostly subfebrile. After two months



Fig. 1. Showing infiltration of the upper half of the left lung. The infiltration shadow are rather dense and distinct. (25/2 1936.)

the patient was transferred to Faxinge Sanatorium where he stayed for 6 months and whence he was discharged as considerably improved. The diagnosis was tub. pulm. vetus?

At the time of admission to the Sanatorium the roentgenogram of the lungs showed infiltration of the upper half of the left lung. Infraclavicularly a couple of peasized cleared up areas. 3 months later: apparently some clearing up of the leftsided process. The infiltration shadows are on the whole dense and distinct. (Fig. 1)

There was moderate anemia which improved on treatment with iron. Otherwise the blood picture presented nothing abnormal. No sputum and the stomach wash was still free from T. B. Mantoux positive with 1/10 mg. The weight increased from 50 to 60 kg. The patient then felt well until the present symptoms set in.

Upon admission to the Medical Department the findings were as follows: Patient very lean and pale. Marked dorsal kyphosis. Some few small slipping lymph nodes in the inguina and the axillae, otherwise no tumour of the peripheral lymph nodes.

Abdomen soft, liver felt about a hand's breadth below the curvature in the midclavicular line, of rather firm consistency.

Rectal exploration: the prostate very slightly enlarged, no nodes. No other noteworthy features.

Other examinations.

Urine + albumin, Esbach 3—12 ‰, Bence-Jones protein found in several examinations, a few times negative. Maximal clearance 26 ml. per min.

Blood: blood urea 71—47 mg % S. R. varied from 140 to 168 mm/t. (Westergren). In sedimentation tubes 550 mm long the S. R. was more than 400 mm/t. Formolgel reaction positive in 20 min. Hemoglobin percentage 48—34, WR. neg.

The differential count exhibited a relative lymphocytosis, thus stab

nuclear leukocytes	0%
polymorphonuclear neutrophilic leuk.	22 »
eosinophilic leukocytes	0 »
basophilic leukocytes	0 »
monocytes	0 »
lymphocytes	75 »
lymphoblasts 2	2 »
plasma cells of lymphocytic type	1 »

In 100 cells was found one erythroblast with a basophilic protoplasm. Leukocyte number 3500 (ranging from 3150 to 5340). Erythrocyte number 2.10—1.38 mil. colour index 1.05—1.22.

Sternal puncture was performed twice. The result of the last puncture was:

Smear	
myeloblasts	0 %
promyelocytes	0.25 »
neutrophilic myelocytes	1.00 »
eosinophilic myelocytes	0.25 »
basophilic myelocytes	0 »
metamyelocytes + stab nuclear leuk.	3.25 »
polymorphonuclear leukocytes	4.75 »

eosinophilic leukocytes	0.50%
basophilic leukocytes	0 »
lymphocytes	22.5 »
lymphoblasts	1.25 »
monocytes	0 »
myeloma cells (1 in mitosis)	18.75 »
myeloma cells of lymphocytic type.....	47.50 »
megakaryocytes	0 »
reticulum cells	0 »
In 400 cells of the «white system» were found erythrogonia.....	0
erythroblasts with basophil. protoplasm.....	8
erythroblasts with eosinophilic protoplasm	9



Fig. 2. Diffuse blurring with striation upwards on the left side and in the lower lobe on the right side. (6/2 1942.)

The picture of the marrow was dominated by cells with a diameter of about 4 microns, i. e. of the size of lymphocytes.

The solidly constructed nucleus is surrounded by a narrow margin of protoplasm. From these cells the transition to typical myeloma cells is seen. It is notably the nuclear type which makes it clear that the small cell belongs to the myeloma series. The histologically treated coagulum exhibits small particles of marrow predominantly consisting of small cells with a diameter the size of the red blood cells or a little larger. The structure of the nucleus is a little coarser than that of the lymphocytes. No typical myeloma cells are seen in the coagulum.

signed Soeborg Ohlsen.

Sputum: No T. B. in 3 examinations.

Feces: Benzidin test negative in several examinations.

Galactose test: precipitated 2.7 g.

Roentgen examination:

Lungs. 1) (ambulant examination before admission). Upwards on the left side and in the lower lobe on the right side is seen diffuse blurring with striation. Both sinus phrenicocostales blurred, especially on the right side.

R. D. pulmonary induration (it was assumed to be a process of a tuberculous nature without fresh processes).

2) 6/2 42. No change in the picture since the last examination (in the mean time the true diagnosis had been made after examination of the bone marrow). Fig. 2.

Bones: partial collapse of the VIII. thoracic vertebra. In the pelvis, os sacrum. upper arm, forearm, thigh-bone, crus, and skull no large local cleared up areas, but the bone structure was somewhat looser than normal.

The patient was discharged at his own request, but was shortly after readmitted, and died after a few days.

Autopsy.

Lungs: Extremely adherent to the thoracic wall. The pleurae interlobares much thickened, fibrous. In the right lung an almondsized cavity filled with yellow pus. In the left lung some small caverns without distinctly marked walls. The changes did not suggest tuberculosis.

Liver: Enlarged, consistency firmer than normal. Border sharp, colour somewhat light tissue more distinctly defined than normal.

Kidneys: Size normal. Capsule somewhat adherent. Cortex not attenuated. Tissue distinctly marked.

Spleen: Somewhat enlarged but not with macroscopically distinct changes in the tissues.

Histological examination of sections of the tissue:

The cells composing the infiltrations range in size from 7 to 20 microns, the smallest cells being the size of lymphocytes. The only peculiar feature is the nuclei, in which the chromatin is seen to be more loosely distributed than in the lymphocytes. The larger cells possess slightly polymorphous nuclei very rich in chromatin, which in some cells are excentrically placed and surrounded by abundant protoplasm which is homogeneous or slightly vacuolised. The cells are sometimes seen around the capillaries, and if so, in a palisade-like arrangement. Some of the atypical cells have two nuclei, some are in mitosis. The cell type at hand corresponds to that found in myelomatosis.

Sections of the pulmonary tissue exhibit some lymph nodes in which the lymphocyte elements are entirely supplanted by the myeloma cells. In addition are seen peribronchial infiltrations consisting of these cells. Some of the alveoli are filled with phagocytic monocytes, others with a coagulum similar to edema. A number of the bronchioli are surrounded by infiltrations of leukocytes and lymphocytes and filled up with the same kind of cells.

Sections of the liver tissue show, especially in the portobiliary spaces, an intense infiltration with the myelomatous cells. The spaces have also increased much in width and the myeloma cell infiltrations extend in between the liver cell trabeculae.

In the spleen the pulp spaces are filled with myeloma cells. The pulp cells are pushed into the background and tend to become fibrocytic.

The renal tissue also exhibits infiltrations of myeloma cells. They are most widely diffused in the corticalis whence they extend into the medullaris. In the neighbourhood of the infiltrations are seen a great many hyaline glomeruli. In some of the convoluted and straight tubules hyaline cylinders are found. The cells in the tubules are swollen and granular. In some places in the medullaris an augmentation of the interstitial tissue is observed. No large precipitates of hyaline material with formation of foreign body giant cells.

Sections of lymph nodes, like the above-mentioned lymph node from the lungs, show an almost complete displacement of the lymphatic tissue.

The congo red reaction revealed no sign of amyloid degeneration.

Sections of the vertebrae after decalcination show the marrow spaces almost filled up with small and somewhat larger myeloma cells. Between these cells were found scattered fat cells, small groups of lymphocytes and cells of the erythropoietic system and the myelocyte series. The lamellae of the spongy bone are very scattered and slender.

signed Soeborg Ohlsen.

Discussion.

The demonstration of the characteristic cells in the bone marrow (4) is of decisive importance for the diagnosis. It was rendered possible by sternal puncture which is the most important procedure in the attempt to diagnose myelomatosis. In some few cases it may fail, but repeated punctures will repay the trouble (12).

As to the nature of the cells most investigators are now agreed, the myeloma cells being at present regarded as more or less atypical forms of the bone marrow plasma cells (14).

Besides by the discovery of the typical cells the case was characterised by several of the features peculiar to myelomatosis, the findings being a greatly increased sedimentation rate, positive formolgel reaction, Bence-Jones protein in the urine, reduced renal function, and anemia.

The very high sedimentation rate would seem to indicate an augmentation of plasma proteins (7, 9), which has indeed been found in several cases.

The picture at hand represents the diffuse form of myelomatosis, which is the most rarely occurring form (10), though it has been reported sometimes from Denmark (8, 9, 14). The typical Kahler syndrome is said to be unusual in this form. (3) Whether the diffuse form and the form characterised by the multiple occurrence of myeloma cells are different stages in the development of the affection has not been settled, no observations being available which favour one or the other view of the matter. (8, 9).

The morphology of the myeloma cells does not seem to bear any relation to the form in which the affection occurs (14).

It is generally stated that the myeloma cells show small tendency to appear outside the bone marrow (5). They are sometimes seen, however, in the liver, spleen, and lymph nodes (6, 11). More rarely infiltration occurs in the kidneys. The myeloma cells are then as a rule found along the vessels, but sometimes also as a diffuse infiltration. Patients suffering from myelomatosis often exhibit symptoms from the lungs. Bronchitis is a frequent feature, and not rarely pulmonary abscesses, chronic emphysema, attacks of asthma, and various forms of pleuritis occur.

Tuberculosis is said to be a rare complication of myelomatosis, and there is not supposed to be any connection between the two affections (5). Austin has reported a case in which there were great changes in the lungs, amongst others calcification. The changes were regarded as tuberculous, but there is no histological examination and no demonstration of tubercle bacilli.

The pulmonary changes are regarded as secondary to the deformities occurring in the thoracic skeleton in myeloma cell infiltrations or the growth of myeloma cells which chiefly involves the ribs and the vertebrae. The pleurites are caused by the invasion of myeloma cells into the pleurae.

Actual infiltrations in the lungs are said to be so rare that e. g. the finding of metastases in the lungs at roentgen examinations is supposed to tell against myelomatosis (13). Whether the present case is an exception that confirms the rule must be left open.

A case of myelomatosis has been described in the literature in which myelomatous metastases were found in the form of a couple of nodules (1). There is, however, no histological confirmation that these elements were composed of myeloma cells.

In the case here reported the changes in the lungs were rather diffuse, involving pathological roentgen findings, a phenomenon not often seen otherwise where there are the usual symptoms of lung affections of the type mentioned above. The pleurites will presumably be visible in the roentgenograms.

The advance of the process could be followed in roentgenograms during several years. The disease seems to have lasted for at least 5 years.

This duration of the disease is longer than in most cases counting the period from the occurrence of the first symptoms until death. A duration of up to twice the number of years has been observed, however (14).

It is not probable that the changes can have been of a tuberculous nature with a secondary infiltration with myeloma cells. A fact telling against tuberculosis is that T. B. were never found in spite of thorough examination at times when the discovery of them could hardly have been avoided if the process were actually tuberculous. In addition the diffusion of the processes that occurred after the admission to Faxinge Sanatorium did not give rise to symptoms that could be interpreted as an activation of a pulmonary tuberculosis.

The febrile pulmonary affection must presumably be explained as pneumonia in the changed tissue, with the development of an abscess.

As previously stated, there were no sure stethoscopic symptoms in spite of the rather considerable roentgenological findings after the last admission.

The Mantoux reaction neither favours nor invalidates the arguments adduced.

The blood picture is in good accord with what is generally seen in myelomatosis (14). There is anemia which is refractory to iron therapy (towards the last). Colour index about 1 or slightly over. Relative lymphocytosis, whilst the total number of white blood cells does not exceed the normal. Plasma cells of lymphocytic type amount to 1 %. Whether any special importance can be attached to the 2 % lymphoblasts considering the heavy encroachment of the process on the bone marrow and lymph nodes, is doubtful. The occurrence of a single erythroblast also agrees with what is seen in anemias from several causes, thus also in myelomatosis.

The present case seems well suited to elucidate the relation between myelomatosis and the so-called plasma cell leukemias.

The rather few cases reported of plasma cell leukemias are characterised by the occurrence of a large number of bone marrow plasma cells in the peripheral blood, sometimes with an increase in the total number of white blood cells, simultaneously with a diffuse occurrence of the same sort of cells in the bone marrow. They differ, in addition, from the usual forms of myelomatosis in that they present a much greater infiltration with plasma cells in the parenchymatous organs.

The case here described does not present anything in the blood picture that deviates from what is common in myelomatosis, but is in a marked degree characterised by plasma cell infiltration of the parenchymatous organs, even to an extent which has hardly been recorded in plasma cell leukemias.

This, if anything, supports the view, which Gormsen too advocates (14), that myelomatosis is of the same nature as the rest of the malignant affections within the myelopoietic system, but that it has small tendency to become leukemic.

Plasma cell leukemia must thus be regarded as a leukemic form of myelomatosis.

Summary.

A case of myelomatosis is reported, with diffuse occurrence of myeloma cells in the bone marrow and extensive infiltrations in the parenchymatous organs, for instance in the lungs.

The relation between myelomatosis, plasma cell leukemia, and the rest of the malignant diseases of the myelopoietic system is briefly discussed.

The view is put forward that plasma cell leukemia is a leukemic form of myelomatosis.

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A Small Laboratory Epidemic of Typhus Fever in Copenhagen.

By

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In the Scandinavian countries exanthematous typhus or typhus-spotted fever is of so rare occurrence that most Scandinavian physicians nowadays have occasion to see this lesion only on travelling abroad.

In 1923 Norgaard gave in *Hospitalstidende* an account of the disease based on his experiences in the first world war as physician to the Danish ambulance in Poland, and in this paper he also gave the data available on the occurrence of the disease in Denmark prior to 1923. Hence it will suffice here merely to mention that the latest epidemic of typhus-spotted fever in Denmark occurred in Copenhagen in 1893, comprising 42 cases, 4 of which terminated fatally. Since then, a dozen solitary and partly doubtful cases have been notified from various parts of the country, the last in 1907 from the island of Bornholm. A review of the annual reports of the National Health Service from 1923 to 1941 shows that during this period no instance of typhus has appeared in Denmark. Under the present war conditions, however, it is rather conceivable that this lesion may become of immediate importance again, and hence we shall here report a small laboratory epidemic under our observation.

which presented some features of interest also with regard to the way of the infection.

In October 1942, in the production of typhus vaccine in the State Serum Institute, 4 cases of the disease occurred.

Case 1.

The first patient was a male physician, 31 years old, who was admitted to the Blegdam Hospital on 8/10/42 (Record No. 5944/42).

About 9 months before, he had commenced working with the production of typhus vaccine, after being vaccinated with phenol-treated «historical virus» (*Rickettsia prowazeki*) cultivated in the yolk sac of hen's egg. He had received 3 injections to which he had reacted with high fever. In September 1942 he went to Frankfurt for instruction in a new method for the vaccine production, and here took part in the intranasal inoculation of mice with a suspension of *Rickettsiae*. After his return home, 28/9, he continued with this work.

On 4/10 the patient felt poorly, and in the night of 6/10 he had fever with several chills, headache and pronounced malaise. The following days the temperature varied between 37.0 and 39.5°, whereafter it had the character of continuous fever round 39° (Fig. 1). On 7/10 he had received an injection of a vaccine prepared from phenol-treated murine virus from mouse liver. This vaccine had been employed previously in several instances without causing any particular discomfort.

On admission the patient was rather severely affected and stated he felt more ill than ever before. The temperature was 39.1, the pulse rate 64,

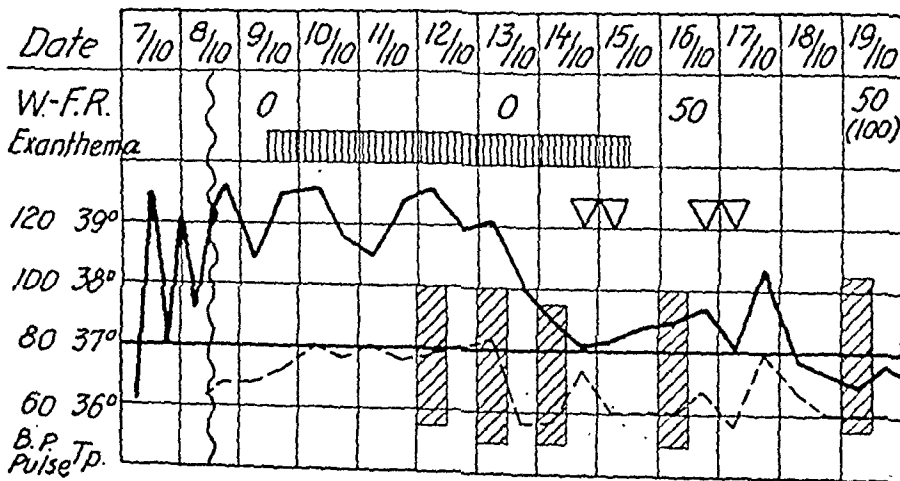


Fig. 1. Case 1: Chart of clinical data. (▽ Attack of cholelithiasis).

regular and strong. Apart from some congestion of the conjunctiva, the physical examination revealed no particular abnormality — in particular, no meningeal phenomena or exanthema.

On the day of admission he had several chills, and next day a rash was seen on the abdomen and the right flank; during the following days it spread somewhat and was most conspicuous on 12/10, when it was seen also on the upper part of the thighs. There was no exanthema of the palms and soles. The rash consisted in scattered, faintly colored, pink spots, varying in size (about lentil size) and reminding of the roseola of typhoid fever; it subsided in 6 days.

The mental habitus of the patient was greatly affected as long as the temperature was elevated. He was irritable, averse to talk to anybody, photophobic and drowsy, complaining continually of violent frontal headache. He slept but poorly, took no food and only a little water, and he was constipated persistently. On 12/10, a few râles were heard over one lung, but X-ray examination showed no abnormality. Gradually his condition was aggravated noticeably, in the morning of 13/10 he was markedly exhausted and drowsy. At noon, however, his condition took a sudden turn, and a few hours after, he was almost feeling well. In the course of 24 hours the temperature fell from 39.1 to 37.5. On 14/10, in the evening, after he had had his supper, he suddenly had an attack of violent colicky pain localized to the top of the epigastrium and accompanied by vomiting. There was marked tenderness in the epigastrium and over the site of the gall-bladder, where the abdominal wall showed defensive rigidity. On 15/10, in the morning, he again had a colicky attack, and this was repeated on 16/10 and 17/10. On 16/10 he presented a distinct jaundice, which persisted till 23/10. The remainder of the convalescence was uncomplicated, and the patient presented no particular after-effect, but complained for a long time of marked tiredness, in particular a rapidly appearing mental tiredness.

Particular examinations: During the febrile period and convalescence the blood pressure was rather low (about 100/55), being lowest on the 16th day of illness: 90/60. Four months later it was 120/60.

During the febrile period the pulse rate was about 80, during the convalescence about 60. The Weil-Felix reaction was negative on 9/10 and 13/10, slightly positive on 16/10: 50; 19/10: 50 (100); 23/10: 50; 28/10: 25, an three months later negative.

Spinal fluid, 9/10: Pressure 240/160, cells 1/3 (erythrocytes 600/3), spinal sugar 56 mg %; Widal, 9/10, 13/10, 16/10: negative; Wassermann negative, Weil reaction 9/10: negative. Blood culture, 9/10: no growth. Sedimentation rate, 19/10: 63 mm, and 26/10: 14 mm. Blood urea, 13/10: 32 mg %. Alkali reserve, 13/10: 25.4 millimol. Plasma color, 16/10: 20, on 26/10: 9. Urine, on admission: no abnormal elements; on 16/10: bile pigment and urobilin. Diastase 1—150. On 21/10 the urine was again normal.

Blood exam., 13/10: hemoglobin 88 %, erythrocytes 4.13 million, color index 1.01. Leucocytes 11,700. Differential count: staff-nuclear

neutrophils 11 %, segment-nuclear neutrophils 63 %, small lymphocytes 18 %, monocytes 8 %.

X-ray exam. of lungs, 12/10: no abnormality.

X-ray exam. of bile passages before and after application of biliselectan showed no shadow of concretions and no gall-bladder shadow on two examinations.

Electrocardiography: no abnormality.

Case 2.

Male, laboratory assistant, aged 29, admitted to the Blegdam Hospital 15/10 (Record No. 6093/42). During the last 9 months he had assisted Pt. No. 1 in the production of typhus vaccine and had been vaccinated three times: about 9 months ago with «yolk sac vaccine», after which he had fever, and twice, 3 months and 1 week ago with «liver vaccine», without any discomfort. Since 1/10 he had assisted in the aforementioned intranasal inoculation of mice, and on 7/10 he had ground some infected mouse lungs in a mortar.

On 13/10 he felt ill with intense headache, chills and rise in temperature to 39.3°. Next day the temperature was 40.1, and from then on it had the character of continuous fever (Fig. 2).

On admission to the Blegdam Hospital, on 15/10, he appeared quite unaffected with a temperature of 40°, pulse 64; and physical examination revealed no abnormality. The patient felt relatively well during the greater part of his illness; only on 20/10 he felt tired and irritable. His appetite was fairly good; the bowels moved slowly. He slept well but complained continually of headache. No rash was observed at any time. In this case

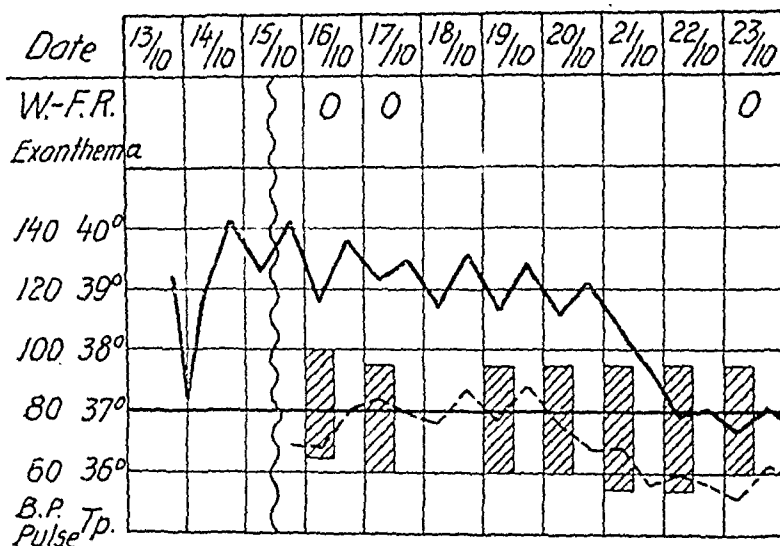


Fig. 2. Case 2: Chart of clinical data.

too, the improvement set in rather suddenly, on 20/10, the temperature falling in 36 hours from 39.2 to 36.8. After this, he soon got well, and was discharged on 29/10, feeling perfectly well.

Shortly after his discharge he had a sudden attack of pain in the epigastrium, accompanied by jaundice. He was admitted to the Frederiksberg Hospital, Dep. E; where X-ray examination of the bile passages after administration of a contrast-giving substance revealed a gall-stone (size of nut kernel). The phenomena subsided rapidly, and the patient has not presented any abnormal features since.

Particular examinations: The blood pressure kept at about 95/55 throughout the period of illness. At discharge it had increased to 110/70; and 4 months later to 125/75.

The pulse rate was about 80 in the febrile period, 60 in the convalescence. The Weil-Felix reaction was negative throughout the course of illness (16/10, 17/10, 23/10, 27/10 and 3 months later).

Spinal fluid, 17/10: Pressure 200; alb. 10; glob. 0; cells 6/3. Widal, 16/10, 17/10, 23/10: negative. Wassermann negative. Blood culture, 17/10: no growth. Sedimentation rate, 17/10: 22 mm. Urine: no abnormal elements.

Blood exam., 19/10: hemoglobin 95%, erythrocytes 4.08 millions, color index 1.09. Leucocytes 10,300. Differential count: staff-nuclear neutrophils 4 %, segment-nuclear neutrophils, 73 %, large lymphocytes 5 %, small lymphocytes 12 %, plasma cells 6 %.

Electrocardiography: no abnormality.

Case 3.

Male, physician, aged 38, admitted to the Blegdam Hospital on 16/10 (Record No. 6113/42). This patient had had nothing to do with the production of typhus vaccine, and he had not been vaccinated. He was occupied with other work in the laboratory where the first two patients came daily, and where infected mouse lungs were ground in a mortar on 5/10 and 7/10.

On 11/10 this patient was taken ill suddenly with chills, headaches, nausea and rise in temperature to 39°. On the following day the temperature rose again, and from then on it had the character of continuous fever round 40°. On 15/10 he noticed some small pink spots on the trunk and arms (Fig. 3).

On admission, 15/10, the patient was rather exhausted. Temperature 39.9. Pulse 100. He stated he felt very ill and complained of a violent headache. The forearms and abdomen presented a rash consisting in scattered, faintly colored, pink spots of lentil size, resembling the roseola of typhoid fever. The conjunctiva was congested; otherwise the physical examination revealed no abnormality. During the following days the rash increased in extension and intensity, being most pronounced on 19/10, when it was seen on the back, chest, abdomen, extremities, including palms

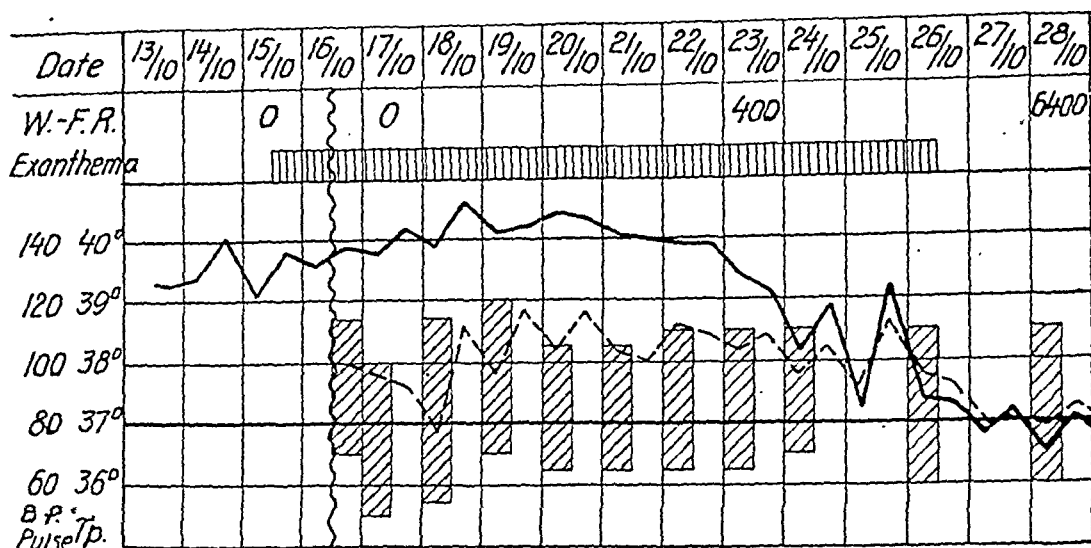


Fig. 3. Case 3: Chart of clinical data.

and soles, but not on the face. After this, the rash subsided, and on 26/10 it had all gone.

During the first days after admission, his general condition was getting worse steadily. He «felt awfully ill», was severely affected mentally, being irritable, photophobic and drowsy, and he complained continually of intense headache. On 19/10 and following days he was somewhat hazy. He took a good deal of fluid but no food; he was constipated; and he could not sleep. On 20/10 a few râles were heard on the back, over the base of both lungs. The temperature kept round 40° for 7 days, and then it fell by lysis in the course of 3 days with great remissions in the morning. After this he improved essentially, but he was still very tired and had difficulty in sleeping. The convalescence was uncomplicated. He was discharged on 5/11.

Particular examinations: The blood pressure was low in the febrile period, round 110/65 (lowest 100/50); on discharge it was 120/60, and 4 months later 120/65.

The pulse rate was about 110 in the febrile period, 80 during convalescence. Weil-Felix reaction, 15/10 and 17/10: negative; 23/10 positive, 400; on 28/10: 6400; on 4/11: 400 (800); and about 3 months later: 50 (100).

Biopsy of the rash (Dr. Fridtjof Bang): In a blood vessel located immediately under the skin, the cells of the adventitia are seen to proliferate, extending out in the surrounding connective tissue, but separated from this and lying like a coat on the wall of the blood vessel, though covering only a part of its periphery (Fig. 4). Between these cells, lymphocytes are seen, and a couple of leucocytes. (The latter do not belong to the characteristic picture, but their presence may presumably be explained by

the circumstance that the lesion here is in its initial stage.) The wall of the blood vessel also shows a characteristic degeneration; in which amorphous degenerated tissue, containing several nuclei, extends into the lumen of the blood vessel and narrows this lumen so that in cross-section it is semi-lunar in outline. This section also shows rather dense cellular infiltration round the other blood vessels, where some of the cells may very well be looked upon as proliferating adventitia cells which in some areas appear to be undergoing slight degeneration. Microscopic diagnosis: Rash as seen in typhus fever.

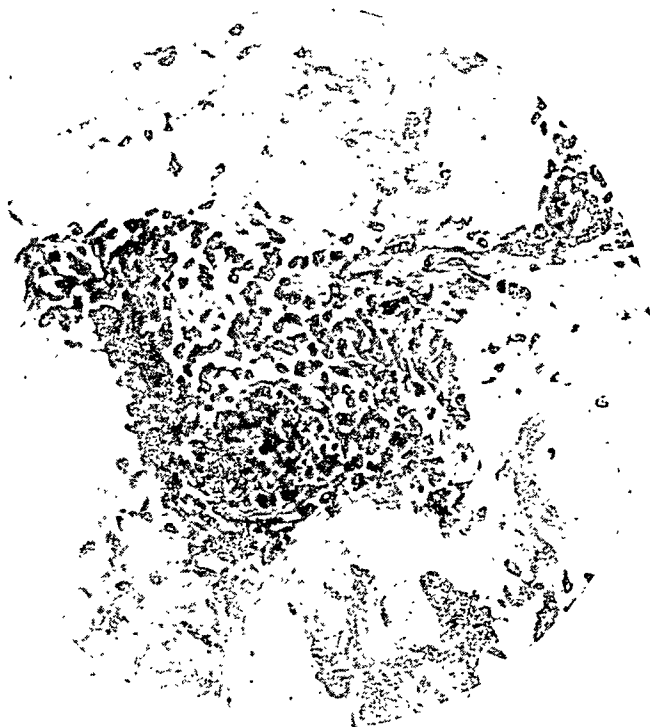


Fig. 4. Microphoto of rash in case 3. For description, see the text.

Spinal fluid, 17/10: Pressure 430; alb. 10; glob. 0; cells 3/3. Wassermann negative. Widal, 15/10, 17/10, 23/10, 4/11: negative. Weil reaction, 19/10: negative. Blood culture, 17/10: no growth. Sedimentation rate, 17/10: 33 mm. Urine: no abnormal elements.

Blood exam., 19/10: hemoglobin 92 %, erythrocytes 4.46 millions, color index 1.02, leucocytes 14,300. Differential count: staff-nuclear neutrophils 10 %, segment-nuclear neutrophils 71 %, large lymphocytes 2 %, small lymphocytes 12 %, monocytes 4 %, plasma cells 1 %. No microorganisms could be demonstrated in blood smears stained with Giemsa.

X-ray exam. of the lungs, 21/10: no abnormality.

Electrocardiography: no abnormality.

Case 4.

Female laboratory assistant, aged 19, admitted to the Blegdam Hospital on 17/10 (Record No. 6139/42). She, too, had had nothing to do with the production of typhus vaccine but was working in the same laboratory as Pt. No. 3. Two months before she had been vaccinated with «liver vaccine».

On 15/10 she was suddenly taken ill with chills and feverish sensations but was still able to do her work. On 16/10 she was given an injection of typhus vaccine («liver vaccine»); in the evening her temperature was 38.4. Next day she felt more ill and had frontal headache, on which account she was admitted to the Blegdam hospital for observation for typhus.

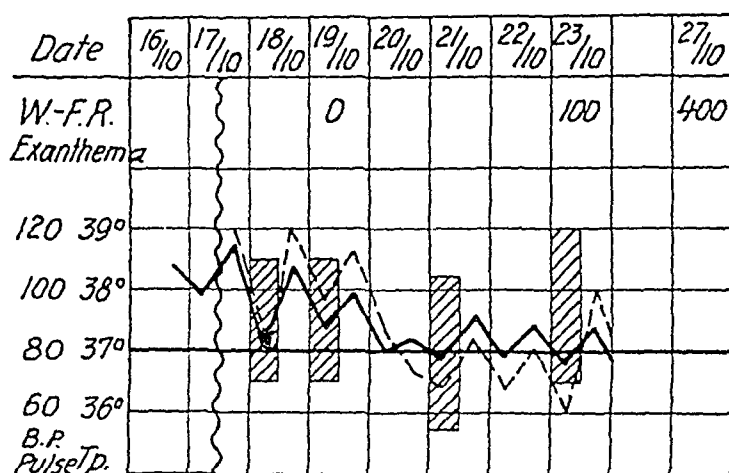


Fig. 5. Case 4: Chart of clinical data.

On admission the patient appeared quite unaffected, but her temperature was 38.2, pulse rate 120. She complained of coryza and headache but did not feel particularly ill. Physical examination revealed no definite abnormality.

She was febrile for 3 days; maximum temperature 38.7, morning remissions to 37 (Fig. 5). Her general condition was quite unaffected throughout the course; appetite, bowel function and sleep normal. No rash appeared.

The convalescence was uncomplicated, and she was discharged on 27/10.

Particular examinations: The blood pressure varied round 115/70; 4 months later, 110/80.

The pulse rate was 120 during the febrile period, 80 during the convalescence.

Weil-Felix reaction: Negative on 19/10; then positive, on 23/10: 100; on 27/10: 400; on 30/10: 100 (200); on 13/11: 50; about 2 months later: 50.

Wassermann negative. Widal, 19/10, 23/10, 27/10, 18/11: negative. Weil reaction, 19/10: negative.

Blood exam., 19/10: hemoglobin 89 %, erythrocytes 4.58 millions, color index 0.93, leucocytes 4500. Differential count: 3 % staff-nuclear neutrophils, 46 % segment-nuclear neutrophils, 2 % eosinophils, 36 % small lymphocytes, 12 % monocytes, 1 % plasma cells. Urine: no abnormal elements.

Electrocardiography: no abnormality.

Discussion.

In our opinion, the diagnosis typhus-spotted fever cannot be questioned in Cases 1 and 3. In Case 3 the diagnosis has to be considered positively established (typical clinical picture, positive Weil-Felix reaction and typical vascular changes on biopsy). In Case 1 the Weil-Felix reaction did not exceed 50 (100), it is true, but the clinical picture was quite identical with that of Case 3 and corresponded precisely to the features described in the literature (typical temperature curve, rash, conjunctivitis, marked cerebral affection, lowered blood pressure, etc.). When, furthermore, in his work the patient has been highly exposed to this infection, the diagnosis has to be regarded as established in this case too.

In Cases 2 and 4 several of the more important symptoms were absent, and if these cases had not appeared in connection with the two preceding, it is not very likely that they would have been imagined to involve exanthematous typhus. Still, in view of their epidemiological connection with the others, we consider also these cases as definite instances of the lesion under discussion. For both cases appeared chronologically in close relation to the two first-mentioned and in persons who certainly may be presumed to have been exposed to the same infection. Apart from a rather typical temperature curve, Pt. No. 2 presented but few symptoms: frontal headache, constipation, decrease in blood pressure and slow pulse rate. Mentally he was affected but very little, he had no rash or conjunctivitis and the Weil-Felix reaction remained negative throughout the duration of illness. In Pt. No. 4 the only symptoms consisted in fever of brief duration and headache. On the other hand, the initially negative Weil-Felix reaction turned definitely positive. In Cases 1 and 2, for further establishment of the diagnosis, guinea-pigs and mice were inoculated with blood and spinal fluid, but the State Serum Institute did not wish to have these animals stabled on its grounds and hence they were killed.

It is generally known that most of the investigators working experimentally with typhus contract the disease sooner or later. Both Ricketts and v. Prowazek died of the disease, and several other investigators have had it — *e.g.*, Zinsser, Mooser, Nicolle, da Rocha-Lima. Of the undoubtedly numerous laboratory cases, however, only few have been reported so far, most often isolated occasional infections. Mooser has briefly mentioned 4 such cases; in one infectious material was splashed in the face of the examiner, and infection followed; in another the infection was produced by an infected Pasteur pipette through a superficial scratch in the skin. In the Pasteur Institute in Tunis, during a number of years, altogether 7 cases of typhus turned up during the work with murine viruses (Nicolle), but nothing was said about the way in which the infection was transmitted. Laboratory epidemics are said to have become more frequent since the work with murine viruses has become more intensive. Such an epidemic due to murine viruses, comprising 15 cases in the Institute for Typhus Fever Research in Krakow has been reported by Eyer, Przybylski & Dillenberg. In 12 of these cases where transmission of the infection by lice could be excluded, the authors ascribe the infection to inhalation of virus-containing louse feces in dust form. In this connection, it is to be mentioned that more recent investigators (Feggin; Starzyk; Blanc & Baltazard) have shown typhus virus in dried louse and flea feces under favorable conditions keeps capable of infections for a much longer time than supposed previously — in some experiments, for nearly two years. With a view to this, many investigators (*e.g.*, Blanc) think that louse feces deposited in clothing constitute a significant reservoir for virus in the inter-epidemic period.

Recently, Löffler & Mooser have reported another laboratory epidemic produced by murine virus in the University Institute of Hygiene, Zurich. The epidemic comprised 6 patients who were all infected while working with intranasal inoculation of mice with emulsions of virus-containing lung tissue. At this work 3 of the patients were provided with gas masks, which they took off as soon as the inoculations were completed. Two other patients were infected while paying a brief visit in the room here employed immediately after the performance of the inoculations. It has to be assumed that the infection here took place through inhalation

of virus-containing droplets and Löffler & Mooser therefore emphasize the necessity of protection by means of gas masks in work of this kind and not to remove them before the room has been ventilated thoroughly.

When murine viruses hitherto have proved more dangerous to work with in the laboratories, according to Löffler & Mooser it is because it has been possible to produce these viruses in far stronger concentrations than the historical virus. Now, however, it is possible in emulsions of typhus-pneumonic mouse lungs to obtain similar concentrations of the historical virus as of the murine; and this fact has already resulted in two epidemics. The first of these was reported from Roumania by Ciuca & Ionescu-Mihaesti, and from Löffler's and Mooser's brief mention of it, it appears to have been of the same character as the epidemic described by the latter and also the epidemic described by us. The second published laboratory epidemic produced by the historical virus is the one reported here by us.

According to statements from the State Serum Institute, in our cases transmission of the infection by lice from the experimental animals is out of the question. Two of our patients (No. 1 and No. 2) have inoculated mice by nasal instillation of a virus containing suspension — a procedure which produces an intense sneezing in the animals, sending forth virus-containing droplets. This has implied the possibility of transmission of the infection by inhalation of droplets or through breaks in the continuity of the skin or by entrance through the conjunctivae. Patients Nos. 3 and 4 were never present at the inoculations mentioned, nor did they ever enter the quarters of these animals. But they have been occupied with other work in a relatively small room where virus-containing mouse lungs twice had been ground with sand in a mortar. With this procedure it can hardly be helped that virus-containing particles of the material splash about. So it seems possible that these two patients may have become infected either by the drop method or by getting infecting material on their hands, or by inhalation of the dried and powderized material.

It has been somewhat difficult for us to explain the weak-positive or absent Weil-Felix reactions in three of our patients as, according to the text-books, the reaction will be positive (*i. e.*, showing a titer higher than 1: 100) in practically 100 % of the cases

after 8—10 days of illness. According to Eyer and collaborators, the reaction will be just as frequent and strongly positive in vaccinated persons acquiring typhus as in non-vaccinated.

In the above-mentioned 15 cases of Eyer and collaborators which all appeared in vaccinated persons, the maximal Weil-Felix reactions were 1:400 and 1:800. These reactions are strikingly weak in comparison to the reactions usually encountered in patients infected by louse bite. Eyer and collaborators think, therefore, that the strength of the Weil-Felix reaction is dependent on the way of infection, so that dust or drop infection is apt to give a less strong reaction. Still, the experiences from the other laboratory epidemics mentioned appear not to lend support to this assumption. In 5 of 7 non-vaccinated persons the Weil-Felix reaction was positive in dilution 1:1600 or higher; in one patient the reaction was negative (Nicolle's second patient), and in the seventh patient (Löffler & Mooser's 3' pt.) the titer was 1:200. But this patient had been treated in the early stage of the disease with convalescent blood. On the other hand, only 2 out of 8 vaccinated patients gave a positive reaction in dilutions higher than 1:800. We are inclined, therefore, to look for the cause of the weak-positive and negative Weil-Felix reactions in our three vaccinated patients in the preceding vaccination.

We shall briefly mention the incubation period which is stated to vary from 5 to 20 days and most often to be 10—14 days. In our four cases, in Pt. No. 1 the incubation period has not exceeded 14 days; in No. 2 it was not over 13 days; in No. 3 not over 8 days, and in No. 4 not over 12 days.

It may be reasonable also to point out that two of our patients presented a complication which we have not found mentioned by any other authors, namely: attacks of cholelithiasis. In Case 2 the X-ray examination showed a negative gall-stone shadow, and in Case 1 the shadow of the gall-bladder after administration of biliselectan was absent on two examinations. Neither patient had ever had any gall-stone phenomena previously.

As to the treatment of typhus with modern chemotherapeutics, no sure experiences have been reported yet (see, for instance, Scheller and Aschenbrenner[. We tried treatment with quinine and lucosil but were not able to see any effect from this treatment.

Summary.

Description is given of a laboratory epidemic of typhus-spotted fever (historical virus), comprising 4 cases. In two cases the mechanism of the infection is presumed to have been drop infection. In the other two, either drop or dust infection. In two of the patients no definite positive Weil-Felix reaction was obtained; and the absence of this reaction is assumed to be attributable to preceding vaccination.

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(From the Biological Institute of the Carlsberg Foundation, Copenhagen.)

The Effect of Dialyzed Serum Proteins and Serum Dialysates on Shock.

By

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In all cases of secondary shock the most serious phenomenon is a reduction in the volume of the circulating blood. This involves a marked reduction in the blood and oxygen supplied to the tissues which in severe cases proves fatal to the individual [Blalock (1), Krogh (2), Moon (3), Koster (4)].

The aim of the therapy, therefore, has been to restore the normal blood volume, and this is accomplished best by intravenous administration of fluid, above all by transfusion of homologous blood or serum.

For the numerous cases of shock arising during a war or in an extensive catastrophe, it naturally will always be difficult to obtain homologous blood or serum in sufficient amounts for the purpose, and numerous investigators have therefore tried to replace these means with other substances that are more easily accessible.

As, according to modern theories, high-molecular colloidal substances should be particularly suitable for this purpose, experiments have been made with solutions of gum arabic, gelatine, starch, pectin — and even with heterologous serum. But the outcome of these experiments has not fulfilled the expectations as it was soon found that these substances were not only almost ineffective

but their administration was often followed by most inconvenient reactions in the patients [cf. Hedenius (5), Hartman, Schelling, Harkins & Brusk (6), Selsø (7)].

Nor have the experiments reported so far with solutions of crystalloids been encouraging, as the fluid introduced in this way leaves the blood stream so rapidly that 50—60 % may be lost already during the injection itself [Køster (4)]. The crystalloids employed for these experiments have been simple solutions, *e. g.*, Ringer solution and physiological salt solution, sometimes with an addition of glucose and bicarbonate.

Tissue culture experiments have shown that dialysates of plasma and serum contain substances of absolutely vital importance to the cells [Fischer (8), Fischer, Astrup & Volkert (9)]. In strongly dialyzed plasma and serum the cells will deteriorate within 24—48 hours. On addition of serum dialysate, the growth of the cells proceeds as in normal culture media, regardless of whether the dialysate originates from a homologous or a heterologous serum. On the other hand, addition of physiological salt solutions (Ringer, Tyrode, *a. s.*) to the dialyzed plasma and serum has no effect whatever.

As dialysates thus contain one or more substances of vital importance to the cells of the organism that positively cannot be replaced by ordinary salts, we decided to investigate whether these dialysates might have some beneficial effect in shock, or whether the good effect of plasma transfusion here was due entirely to the protein content of the plasma.

Experimental.

The experiments were carried out on rabbits, mostly white rabbits, purchased on the ordinary market.

For production of the shock we decided to employ a severe loss of blood, as in this way it is easier to graduate the shock and, besides, by observation of the blood pressure, to obtain a fair impression of whether the injected fluids remain in the blood stream.

The bleeding of the animal was performed, under urethane anesthesia, from the femoral artery. The blood pressure was measured with a mercury manometer, connected with the carotid artery. The fluid injections were given through a cannula inserted permanently

in the jugular vein, in order to avoid the sensitive reactions on the blood pressure produced by repeated introduction of a needle.

It was soon found that in order to obtain reliable results it was necessary at the bleeding to remove a considerable amount of blood, as otherwise the blood pressure showed a tendency to a spontaneous rise — something which naturally would give quite misleading results. Really, several investigators have failed to pay sufficient attention to this fact, and many divergent and often misleading results are undoubtedly due to this circumstance. In order to produce a sufficient fall in blood pressure and ensure against a spontaneous rise in blood pressure, in our experiments the bleeding was carried out in several stages within about $\frac{1}{2}$ —1 hour. In this way it was possible to produce a fall in blood pressure from 130 mm to 40 mm Hg without collapse of the animal and also to keep the blood pressure practically constant at the low level for a considerable length of time. Only when this stage was reached could the experiments commence, and now the variations in the blood pressure afforded a measure for the therapeutic value of the fluids injected. In every instance the injected amount of fluid was equal to the amount of blood evacuated.

The dialysates were prepared by dialysis of ox serum at 0° in cellophane tubes against an equal volume of distilled water; a small amount of chloroform was added both to the inner fluid and to the outer. After dialysis for two days the dialysate was concentrated to half its volume in vacuum. After neutralization with $1/n$ HCl, sterile filtration through a Seitz asbestos filter.

As a control for the good effect that might be obtained the animal was first given a transfusion with homologous plasma. The effect of this took the form of an abrupt rise in blood pressure from about 40 mm to 90 mm Hg, and this was then followed by a slow gradual rise to about 110 mm, whereafter the blood pressure kept constant at this level for several hours.

The effect of an injection of dialysates of serum or plasma resembled at first that of plasma injection as on rapid injection it also showed an abrupt rise in blood pressure up to about 70 — 80 mm, but here the effect was very brief, the rise being followed within a few minutes by a fall. At first this fall was rather abrupt but it soon became slow and gradual, reaching the initial level in about 40 min. Not even a fairly protracted effect was obtained in any instance.

In order to see whether these dialysates might prove more beneficial than ordinary salt solution, Ringer solution was employed in some cases. The variations in the blood pressure produced with Ringer solution were almost identical with those obtained by injection of the dialysates, and hence nothing is gained by employment of the dialysates instead of ordinary salt solution.

As thus the dialyzable substances of the plasma were ineffective, an experiment was made to ascertain the effect of solutions of purified plasma proteins.

In order to obtain a solution which contained only plasma proteins, 50 ml of citrated rabbit plasma was precipitated with 200 ml of a saturated ammonium sulphate solution. Filtration overnight at 0°. On the next day, the precipitate is dissolved in 30 ml of water. Dialysis in cellophane membrane against running water for four hours, then overnight against Ringer solution with addition of a little toluene. On the following day the solution is coagulated, and the fibrin is removed by stirring and centrifuging. Volume 40 ml; dilution with physiological salt solution to make 50 ml; sterile filtration. Thus, in its protein content the solution obtained corresponds to the plasma, while all the low molecular substances have been removed by precipitation and dialysis.

When such a solution was used for transfusion, it was found to have almost the same effect as that of ordinary plasma transfusion, producing a high constant blood pressure of about 100 mm Hg.

From these findings the conclusion is drawn, that the effect of plasma and serum transfusion in shock is due exclusively to its protein content, probably on account of the Donnan effect.

A survey of the experiment here reported is given in Table 1.

Table 1.

The effect of the different solutions on shock produced by loss of blood.

Solutions infused	Blood pressure at different junctures after the injection.				
	Before inj.	10 min.	20 min.	40 min.	2 hours
Rabbit plasma ...	39 mm. Hg	92	102	110	109
Serum dialysate ...	43	83	60	50	45
»Ringer» solution .	41	77	56	46	—
Protein solution from rabbit plasma	40	85	96	104	100

Summary.

It is demonstrated that, while dialyzates of serum are ineffective in shock, a good effect is obtained with the isolated and purified plasma proteins.

This work was carried out with the aid of grants from »Løvens kemiske Fabriks Legat til Minde om Apoteker A. Kongsted and from »Danmarks tekniske Højskoles Fond for teknisk Kemi».

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Studies on Serum Bilirubin.

Analytical Methods and Normal Values.

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(Submitted for publication July 26, 1943).

Our Knowledge about the normal values of the serum bilirubin is mainly based on older investigations carried out either with non-specific methods of analysis (*e. g.*, determination of the icterus index) or with non-quantitative diazo methods; to the latter all diazo methods using protein precipitation by alcohol and filtration are to be reckoned, as bilirubin is adsorbed in varying degree to the precipitate and the filter, and accordingly, the serum bilirubin concentration found can be considerably lower than the actual.

The only methods described so far by which these analytical errors are totally avoided are the methods of Jendrassik and Cleg-horn (1937) and the more simple and accurate modification of this method given by Jendrassik and Gróf (1938). Here all precipitation and filtration is avoided by using a caffein-buffer solution as catalysator for the diazo reaction instead of alcohol. Also Malloy and Evelyn (1937) have worked out a method in which the precipitation is avoided by diluting the serum ten times before the addition of the alcohol; this method, however, suffers from drawbacks owing to the great dilution causing difficulties in the photometric readings of low bilirubin concentrations, and the values obtained by this method are lower than those obtained with Jendrassik and

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Gróf's method (cf. With, 1943) for which reason the method of Malloy and Evelyn is to be considered as inferior to Jendrassik and Gróf's.

The last-mentioned method is very simple to carry out, and a trained laboratory technician is able to learn it rapidly. It takes 15 minutes to do a single analysis, but if one has more than one at the same time it can be done by using 5—10 minutes per analysis. Moreover the method can be used as micromethod and carried out on cutaneous blood (0.1 ml serum). As the technique has not previously been described in English, it is to be given here. As to the theoretical foundation of the method the reader is referred to previous papers of the author (With, 1942, 1943) and to papers of Jendrassik and co-workers.

Description of the Technique of Analysis.

Reagents: Caffein reagent consisting of 20 g caffein, 30 g sodium benzoate and 50 g of sodium acetate dissolved in water and diluted to 400 ml. — *Ehrlich's Diazo reagent:* 1) 1 g of sulfanilic acid and 15 ml of concentrated hydrochloric acid diluted to 1 liter; 2) 0.5 g of sodium nitrite diluted to 100 ml. The solutions 1 and 2 are kept separate, and just before the performance of the reaction the final reagent is prepared by mixing 10 ml of 1 and 0.25 ml (6 drops) of 2. — *Alkaline buffer solution:* 10 g sodium hydroxyde and 35 g potassium-sodium tartrate diluted to 100 ml.

Procedure: 1 ml (in the micromethod 0.1 ml) of serum or plasma — after With (1942) the bilirubin concentration is the same in plasma and the corresponding serum — is mixed with 2 ml. (0.2 ml) caffein reagent, and 0.5 ml (0.05 ml) diazo reagent is added and thoroughly mixed, and the time is noted. 10 minutes later 1.5 ml (0.15 ml) of the alkaline buffer solution are added (by which the original red color following the addition of the diazo reagent becomes blue). Within 10 minutes the blue — or, in the case of low bilirubin concentrations, green — color is read in the Pulfrich photometer with filter S. 61 in a layer of thickness of $\frac{1}{2}$, 1 or 2 cm according to the color intensity. If the micromethod is used, special cuvettes are required, either microcuvettes or — more conveniently — the so-called »Kleinkuvetten».

If the greatest possible accuracy is wanted, the use of control solutions — which are to be placed in the second cuvette of the photometer — is necessary; in other cases the reading is simply made with water in the second cuvette. The control solution is: 1 (0.1) ml serum + 2 (0.2) ml. caffein reagent + 0.5 (0.05) ml. »diazo blank» + 1.5 (0.15) ml. alkaline buffer. By »diazo blank» is meant a solution containing 15 ml. concentrated hydrochloric acid in 1 liter. The control solution eliminates errors

from opacities in the serum and other colored substances. In the case of icteric sera the use of control solutions is unnecessary.

The calculation of the bilirubin concentration — in mg. per 100 ml. serum — is made by means of the following formulas:

(1) $c = 5.32 (e - k)$; (2) $c = 5.35 (e - k - 0.025)$; in which c is the concentration, e the extinction by filter S. 61 in the layer of thickness 1 cm. and k a constant determined by the reagents. The formula (1) is used in readings with control solution while (2) is used in readings without.

The constant k is determined by adding 2 ml. caffein reagent and 1 ml. diazo reagent to 1 ml. distilled water and, 10 minutes later, adding 1.5 ml of the alkaline buffer solution, after which the resulting green color — diazo reaction of the caffein — is read in the layer of thickness 1 cm. with S. 61. The read extinction divided by 5 then gives the value of k for the reagents used; k usually lies about 0.010.

In the case of icteric sera dilution (1:5—1:20) often is necessary to avoid colors too strong to allow an accurate photometric reading. Here one also has to use the formula (1) for the calculation even though control solution is not used (the reason for this is that opacities and other colored substances are of no importance in icteric sera).

If the method is to be used as a micromethod, special small glass and fine pipettes are to be used and the reading carried out by means of special cuvettes (microcuvettes or, better, «Kleinkyvetten»). A detailed description of the technique of the micromethod is given by With (1942, 1943).

The accuracy of the method is good; thus With (1942, 1943) found the difference between double analyses below 0.05 mg per 100 ml in the great majority of cases. In the case of icteric sera, however, this limit of error has to be multiplied by the number of times the serum is diluted before analysis.

The Relation of the Method to Older Analytical Methods.

As errors from protein precipitation and adhesion to filters are avoided with the described modification of the diazo method, it is easily seen that it must give higher values than diazo methods using alcohol as a catalysator (e. g., the classical v. d. Bergh method, Heilmeyer and Krebs' and Haslewood and King's methods). That this really is the case is demonstrated by the fact that normal values for the serum bilirubin lie higher with this method than when the other methods are used (cf. below). It is, however, to be emphasized that the difference between the Jendrassik and Cobb method and older diazo methods presumably is considerably more pronounced in the case of «direct» bilirubin reaction than in the case of «indirect», as v. d. Bergh (1924) found that the latter form of

bilirubin was adsorbed to the protein precipitate to a considerably lesser degree than the first.

The relation between Jendrassik and Gróf's method and the almost universally used method of icterus index determination is of special interest. Without underrating the great practical value of the simple and rapid icterus index method, one cannot deny that this method can hardly yield more than rather rough approximations of the serum bilirubin concentration in the case of normal

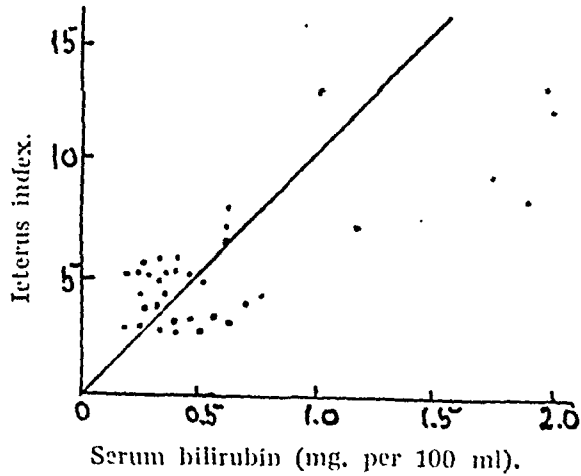


Diagram 1. 35 normal or slightly icteric sera.

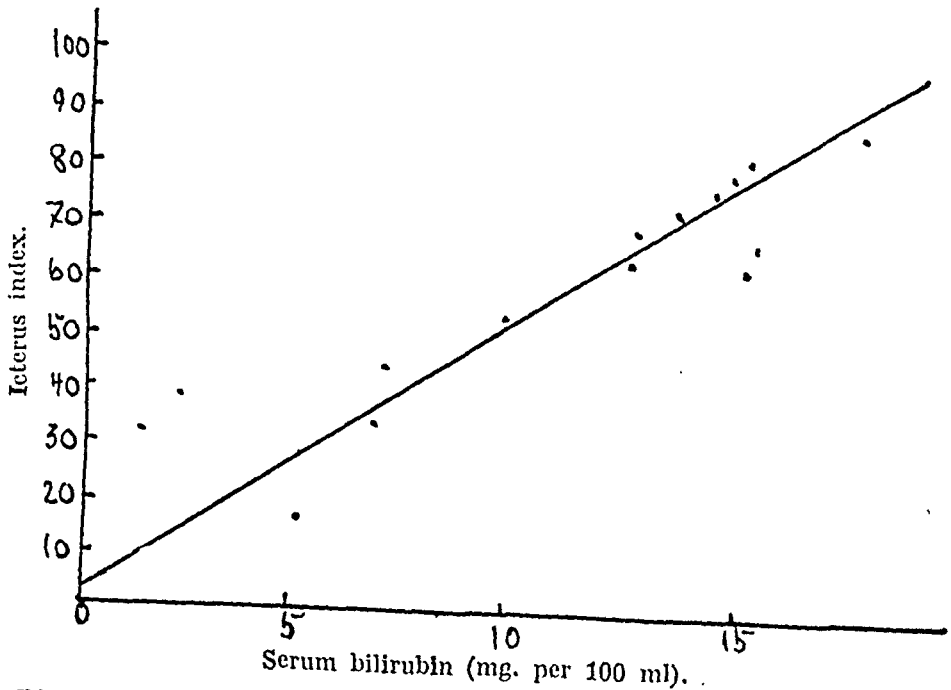


Diagram 2. 15 icteric sera. Author's own measurements of icterus index.

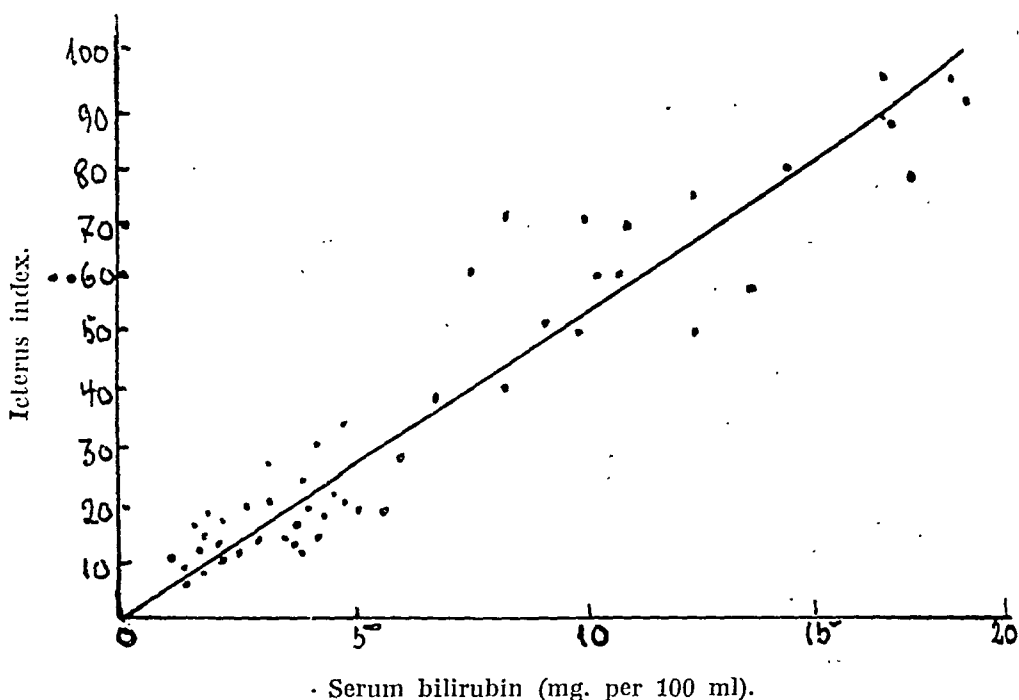


Diagram 3. 50 icteric sera.

or slightly icteric sera, as unavoidable opacities and other yellow colored substances as carotenoids may cause considerable errors. This is illustrated by comparison of determinations of the icterus index and serum bilirubin on the same sera as seen in Diagrams 1—3; here the icterus index is placed along the vertical axis and the serum bilirubin along the horizontal. Diagrams 1 and 2 are plotted on the basis of the author's personal readings of both icterus index and serum bilirubin while in Diagram 3 the icterus index determinations were carried out by the routine clinical laboratory.

From these diagrams it is readily seen that the correlation between icterus index and serum bilirubin is very poor in the case of normal and slightly icteric sera; in the case of medium-icteric sera the correlation is reasonably good and only for strongly icteric sera a really good correlation is found. On the basis of these findings it seems justified to declare that it is impossible to conclude from icterus index to serum bilirubin concentration when the icterus index is below 20. Thus an icterus index below 7 says only that the serum bilirubin is normal but is of no significance when we are interested in the bilirubin concentration within normal

limits, and an icterus index of 15 means only the presence of slight icterus but is only of very limited value as a measure for the degree of this slight icterus.

The diagrams also call for caution in setting up rigid limits for the normal values of the icterus index, as the icterus index method is very inaccurate in the zone of the normal limit, and the serum bilirubin in normal persons shows a broad zone (1.0—2.0 mg per 100 ml) of values which may be normal but most often are to be regarded as pathological (cf. below). So, it cannot be correct to speak of a single value for the icterus index as the limit between normal and pathologic values.

Previous Investigations of the Serum Bilirubin in Normal Persons.

V. d. Bergh (1918) found in the majority of normal persons between 0.25 and 0.40 mg per 100 ml. in the serum (1: 400,000—1: 250,000), but states that it is not unusual to find values between 1.1 and 1.3 mg per 100 ml (1: 90,000—1: 80,000). He gives, however, no description of the composition and size of his normal material. Lephene (1920) found the average value 0.15, Mandelbaum (1922) found the value 0.25, and Haselhorst (1921) 0.5 mg per 100 ml for the upper limit. Bozian (1920) usually found values below 0.75 mg per 100 ml., but occasionally higher values in normal persons. Sivo (1927) found — among 200 normal persons — values between 0.80 and 1.10 mg per 100 ml and regarded values above 1.20 as pathological. Most commonly 1.0 mg per 100 ml is regarded as the upper normal limit (cf. *e. g.*, Forster, 1925). Among more recent investigations, Brochner-Mortensen's (1935) and Vaughan and Haslewood's (1938) are to be mentioned. The first author determined the serum bilirubin in 78 normal persons with the method of Heilmeyer and Krebs (1930) — a diazo method including alcohol precipitation and filtration and reading in the Pulfrich photometer — and found values between 0.15 and 0.92 mg per 100 ml with the great majority lying between 0.20 and 0.60. On examination of 100 normal persons and using the method of Haslewood and King (1937) — a diazo method with alcohol precipitation and filtration — Vaughan and Haslewood (1938) found values between 0.20 and

1.70 mg per 100 ml with the mean value of 0.54; a distribution curve is given which is distinctly asymmetrical and of the same nature as the one found in our material (cf. below). Moreover, a similar asymmetrical distribution is found when a curve is drawn on the basis of Bröchner-Mortensens material (cf. his table, p. 7).

Finally, a few investigations with fully reliable methods have been carried out. Thus Jendrassik and Cleghorn (1937) state that about half of the normal persons examined by them showed serum bilirubin concentrations between 0.60 and 1.0 mg per 100 ml, but they do not mention the number of persons or other details. Vahlquist (1941, p. 154—158), employing Jendrassik and Cleghorn's method on 80 normal persons (38 men, 42 women) between 20 and 30 years, found values ranging from 0.34 to 1.67 (average 0.82) mg per 100 ml. in the men and from 0.34 to 1.60 (0.63) in the women. He gives, however, no distribution curve or tables from which one may be plotted. On the other hand, he mentions that he found values of 1.07—1.87 mg per 100 ml in 10 normal school children and in one case even 2.28; in the last-mentioned case the hyperbilirubinemia apparently was familial, as two brothers showed 2.07 and 2.72. In the other 9 children, however, the relatives did not show values above 1.19 mg per 100 ml.

Summarizing, one may say that older investigations give a very variable and unsatisfactory picture of the normal values for the serum bilirubin. More recent materials, however, all show a pronounced asymmetrical distribution of the normal values with a rather sharp fall towards the low values and a more gradual fall towards the high, and — what is essential — a small but definite number of normal persons with values considerably above the average value and the great bulk of the other values. This last phenomenon was, by the way, already mentioned by v. d. Bergh, who found a certain number of high physiologic values. The conclusion will be that we cannot accept 1 mg per 100 ml as the upper normal limit of serum bilirubin and that further investigations on the normal values and their distribution carried out with fully reliable methods are needed.

Own Investigations on the Serum Bilirubin in Normal Persons.

Our material consists of 100 normal persons, aged between 20 and 35 years, 50 men and 50 women, most of them medical students and nurses. Further, determinations were carried out on 200 medical patients — either patients from the medical department or from the dispensary — free from diseases of the liver and bile passages and from hemolytic anemia. All determinations were carried out in serum with the analysis described above. Our results are presented in Table 1, and the distributions of the 200 patients is illustrated by Diagram 4 in order to show the asymmetry. The normal persons show practically the same distribution, which therefore is not illustrated graphically.

Table 1.

The Serum Bilirubin in Normal Persons and Medical Patients.

Serum bilirubin concentration (mg. per 100 ml):

<0.10	0.10-0.20	0.20-0.30	0.30-0.40	0.40-0.50	0.50-0.60	0.60-0.70	0.70-0.80	0.80-0.90	1.00-1.10	1.10-1.20	1.20-1.30	1.30-1.40	1.40-1.50	1.50-1.60	1.60-1.70	1.70-1.80	1.80-1.90	>1.90
1) 50 normal men; number of cases:																		
0	2	3	6	5	6	8	6	8	0	1	1	1	1	0	0	0	0	0
														Average: 0.71 mg per 100				
2) 50 normal women; number of cases:																		
0	1	3	6	4	8	7	4	6	4	1	1	2	0	0	0	0	1	1
														Average: 0.69 mg per 100				
3) 200 medical patients without injury to the liver or bile passages or hemolytic anemia; number of cases:																		
0	5	18	23	22	20	24	23	17	20	7	8	3	2	1	1	0	2	1
														Average: 0.67 mg per 100				

From Table 1 it is seen that at the highest 1 % of normal persons shows a serum bilirubin concentration above 2.0 mg per 100 ml, as values above this limit were not found among the normal persons, whereas 2 of the 200 patients showed such values. It is further seen that only ca 5 % of the normal persons have values above 1.5 mg per 100 ml and ca 13 % above 1 mg per 100 ml. The mean values for the serum bilirubin concentration was 0.71 mg per 100 ml for normal men, 0.69 for normal women and 0.67 for the patients. On calculation of the mean value for the 60 patients over 50 years among the 200 a mean value of 0.65 is found. So, sex and age do not seem to have influence upon the serum bilirubin concentration.

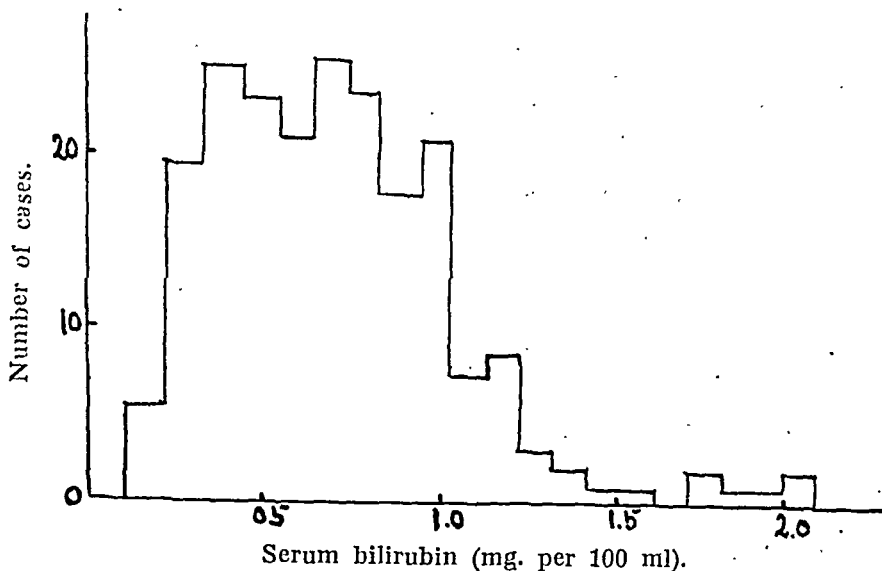


Diagram 4. Distribution of the serum bilirubin in 200 medical patients.

As the distribution curve is asymmetrical, one might say that the mean value is not the most suitable statistical parameter. The median would, of course, be a better expression. But the medians of the distributions in the material are not very different from the mean values; so, the median of the distribution of the 200 patients is 0.76 mg per 100 ml, the median of the 50 men 0.76, and that of the 50 women 0.75 mg per 100 ml.

Further, it would be of interest to see if we might arrive at a symmetrical distribution by taking the logarithms. By using the logarithms of the serum bilirubin concentrations instead of the concentrations themselves it is readily seen that the part of the curve corresponding to the high values of the serum bilirubin would be considerably shortened; but at the same time the other part of the curve becomes longer, and it is thus still asymmetrical.

One might be inclined to think that the «normal» persons of the material showing the highest values for the serum bilirubin really were suffering from latent diseases of the liver. It is, of course, difficult to deny that this may have been the case in a few instances, but as so many as 5 % showed values above 1.5 mg per 100 ml — i. e., more than two times the mean value — it must be regarded as very unlikely that all the persons showing values in the extreme right of the distribution curve were suffering from disturbances in the liver function, hemolytic anemia or diseases of the bile passages. For such an assumption would force us to regard at least 5 % of the normal persons to be suffering from the diseases mentioned.

Remarks on Physiological Hyperbilirubinemia (Icterus intermittens juvenilis).

According to the discussion above the most plausible explanation of the asymmetrical distribution curve for the serum bilirubin in normal persons — as found by Brochner-Mortensen and Vaughan & Haslewood as well as by us — is to assume that the high values really are high normal values. So we have to be prepared to find some normal persons with serum bilirubin concentrations considerably above the average level. By the way, this has long been known, as v. d. Bergh (1918) mentioned such cases under the name »physiologische Hyperbilirubinämie». A further argument in favor of looking upon these high serum bilirubin concentrations in normal materials as physiologic hyperbilirubinemia is that all transitional values between the majority of normal values and the highest of the »physiological hyperbilirubinemia» are represented in the normal materials; for, if the high values were characteristic of a pathological state, we would expect that these high values were clearly separated from the normal values.

In this connection it is natural to discuss the nosological entity »*icterus intermittens juvenilis*» described by Meulengracht (1938), as it lies near to suppose that these cases are to be found among the 5 % of normal persons showing values above 1.5 mg per 100 ml. On the other hand, all these high normal values cannot belong to the group *icterus intermittens juvenilis*, as this condition is rather rare, according to the description of Meulengracht. Still, as Meulengracht selected his cases with clinically visible jaundice as criterion, it is easy to understand that only the very highest values of the asymmetrical distribution curve can have any chance of being regarded as *icterus intermittens juvenilis* *i. e.*, as normal persons with extremely high values of serum bilirubin. This view on the condition *icterus intermittens juvenilis* is in good agreement with the favorable outlook in Meulengracht's cases. Further, it is to be remembered that clinical jaundice is not determined by the serum bilirubin level alone, as the threshold value of the serum bilirubin for visible jaundice shows some individual variation (With 1943), and for this reason, a high physiological level of the serum bilirubin as well as a low threshold for visible jaundice is required in order to be regarded as having *icterus intermittens juvenilis*.

The investigations of Meulengracht on this condition are of special interest as they seem to show that these cases maintain their high serum bilirubin level through periods of several years — a circumstance which perhaps is not confined to the high values of the serum bilirubin and might lead to the assumption that the serum bilirubin level is a rather fixed value

characteristic of the individual and maintained throughout the years. Future researches will have to find out whether this view is correct or not. As Meulengracht has only found the condition *icterus intermittens juvenilis* among young persons, one might feel inclined to think that the serum bilirubin level was declining when middle age was passed; but this observation of Meulengracht might also be explained in other ways (e. g. elevation of the threshold of the serum bilirubin for visible jaundice with advancing age).

Finally it is to be stressed that we have to be somewhat cautious in making the diagnosis *icterus intermittens juvenilis* as we always have to think of oligosymptomatic chronic hepatitis as well, and the differential diagnosis between these two conditions is often very difficult — and of course of great interest with regard to the prognosis. In such cases the liver biopsy can be of value, and in some cases of *icterus intermittens juvenilis* it has shown normal histologic pictures (Roholm, Krarup and Iversen, 1942), but it is to be pointed out that it is possible that in other cases with the same clinical symptoms it may show chronic inflammation.

Summary.

The serum bilirubin concentration in normal persons requires further investigation because the analytical methods used in works on this subject cannot be regarded as fully reliable. The diazo method of Jendrassik and Gróf (1938), previously published only in German, which is quantitative as well as specific, is described. Comparison is made of determinations of the serum bilirubin by this method and icterus index determinations and shows that the icterus index is a rather inexact expression for the serum bilirubin concentration (cf. Diagram 1—3). The serum bilirubin concentration is determined in a material consisting of 50 normal men, 50 normal women and 200 medical patients without injury to the liver or bile passages or hemolytic anemia (cf. Diagram 4 and Table 1). The problem of physiological hyperbilirubinemia and its connection with the so called «*icterus intermittens juvenilis*» (Meulengracht) is discussed.

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Case of Coronary Thrombosis — a Contribution to the Discussion of the «Silent» Electrocardiogram.

By

KNUT LIEDHOLM.

(Submitted for publication July 12, 1943).

The surest way to diagnose a cardiac infarction is by electrocardiographic examination, which does not only indicate the eventual presence of an infarction but also its localization — the knowledge of which is of no small importance for the just valuation of the symptoms in an individual case.

In not a few clinically typical cases (also verified after necropsy) we find however none of the characteristic electrocardiographic changes usually present in cases of infarction. The electrocardiograms, obtained in such cases, have therefore sometimes been called «silent». In some cases this has been explained as being due to a simultaneous infarction of the anterior and the posterior ventricular wall, during which the electrocardiographic changes, caused by these two types of infarction and pointing in opposite directions, would cancel each other, thus making the electrocardiogram seemingly normal. In other cases it has been conjectured that the infarction might be localized to a «silent» zone. The existence of such «silent» zones has been verified in dogs, but as yet not with certainty in man.

In the Lund Medical Clinic we have had the opportunity of observing one case which easily might have been registered as a «silent» infarction, if not especially favourable circumstances had been at hand. As it is, this case points to other possible explana-

tions than those mentioned above of why the electrocardiographic examination sometimes fails.

Case report: J. 2404/36. A. J., medical attendant at the St. Lars' Hospital, 48 years old. Hereditarily nothing of interest, perhaps with the exception of his father's death of a renal disease. The patient was married and had a healthy child. He had not had rheumatic fever, chorea minor or lues. He had always been in good health until 6 years before his admittance to the hospital, when he got epidemic parotitis with orchitis.

The last three years he had been troubled periodically with attacks of pain in the chest especially after exertion. He had also begun to suffer from breathlessness during work. As these symptoms began to be more pronounced about a year ago, the patient sought a doctor. His blood pressure was 210/120 mm Hg, and the heart enlarged to the left with a soft systolic murmur over the apex and accentuated A_2 . The patient's blood pressure varied during the following year between 180/100 and 240/150 mm Hg and as his subjective state was not markedly improved by the prescribed regimen, he was admitted to the Lund Medical Clinic. Nothing in the anamnesis pointed to the presence of a clinically manifest cardiac infarction.

State of the patient on admission to the Med. Clin., Lund, Oct.

General state good. Flesh and muscles in good condition. No cyanosis. No dyspnoea in rest. No oedema.

Heart: left cardiac border 1.5 cm outside the mammillary line. Right cardiac border in the sternal line. Systolic murmur over the apex. A_2 slightly accentuated.

Lungs and abdomen normal.

Blood pressure 195/125. Wassermann reaction negative. Sedimentation rate 16 mm/60 min.

Haemoglobin 90 per cent. Erythrocyte count 4.4 million, leucocyte count 8,100.

Venous pressure 2.5 cm H_2O . Vital capacity 3 100 cm^3 .

Roentgenological examination: The maximum transverse diameter was 16.5 cm, of which 12 to the left of the midsternal line. Corresponding width of the chest 27.5 cm. The roentgenological examination revealed distinct enlargement of the arterial ventricle. No enlargement of the auricles. Pulmonary fields normal.

Electrocardiogram: P-Q interval 0.10 sec. P_{III} negative. Distinct Q_{II} and Q_{III} . Depression of the S-T segment in Leads I and II. Negative T waves in all leads. Diagnosis: Auricular rhythm. Coronary insufficiency and hypertrophy and dilatation of the left ventricle (fig. 1).

The patient was kept at rest in bed. The first week was uneventful, and a second electrocardiogram was taken (Oct. 16, 12 a. m.). On comparison with the electrocardiogram taken at admission no changes could be found (fig. 2).

In connection with a laborious defaecation 1 1/2 hour after this

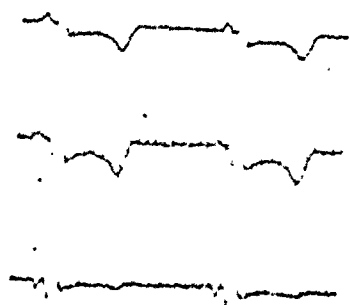


Figure 1. Oct. 10.

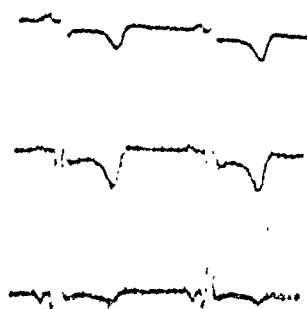


Figure 2. Oct. 16, 12 a. m.

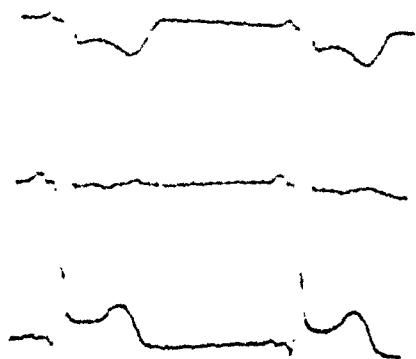


Figure 3. Oct. 16, 2 p. m.



Figure 4. Oct. 16, 7 p. m.

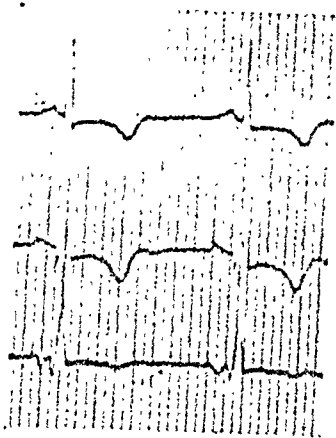


Figure 5. Oct. 17, 1 p. m.

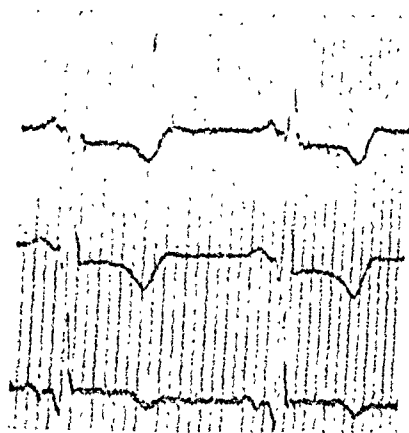


Figure 6. Dec. 1.

Fig. 1—6. Electrocardiograms. Leads I, II and III registered synchronously.
Time $\frac{1}{20}$ sec.

examination the patient turned sick, vomited and transpired profusely. No cardiac pains. Muffled heart sounds. Pulse rate 40/min. Blood pressure 90/55—80/50.

An electrocardiogram was taken half an hour after the patient fell ill. This showed distinct changes pointing to a dorso-basal cardiac infarction. High take-off of the S-T segment in Lead III. T_{III} now positive (fig. 3).

After the initial severe collapse, the patient recovered within some hours. At 8 p. m. the blood pressure was 160/90 and the temperature had risen to 37.8°. The temperature reached a maximum (39.2°) in the afternoon of Oct. 18. Leucocyte count (Oct. 17) 10,600. Oct. 21 sedimentation rate 63 mm/60 min.

A third electrocardiogram was taken already at 7 p. m. the same day the attack set in, revealing less distinct changes. The high take-off of the S-T segment in Lead III now less marked. T_{II} once more negative (fig. 4).

Another electrocardiogram (fig. 5), taken the following day at 1 p. m. is similar to those taken before the onset of the attack, (fig. 1 and 2). All signs of a recent coronary occlusion have disappeared.

The patient recovered steadily. The temperature sank by and by and from Nov. 5 it was normal. On Nov. 25 the sedimentation rate was 36 mm/60 min. On Dec. 2 the patient was dismissed from the hospital, being then subjectively free from complaints. Blood pressure at that time 170/105. Roentgenological examination of the heart showed no changes when compared with the state at admission. The electrocardiogram was similar to that taken at admission.

One morning about seven weeks after the patient left the hospital, he was found dead in his bed.

Clinical diagnosis: Essential hypertension + Coronary sclerosis + cardiac myodegeneration + cardiac infarction (dorso-basal infarction).

Post-mortem examination: (Dr Alf Sjövall). . . Heart hypertrophied both to the right and the left, especially the latter, dilated, flaccid. Normal pericardium. No embolus in the pulmonary artery. No valvular changes. In all coronary arteries numerous, diffuse, calcified atheromatous plaques narrowing the lumen. The ram. circumflexus of the left coronary artery can simply not be clipped. It has been converted to a hard string, crackling when cut. Corresponding to this branch there is at the base of the heart, to the back and somewhat laterally, an enormous heart infarction, which is peripherally already fibrously white and centrally gelatinously gray-red. The infarction does not quite reach the apex and leaves the anterior ventricular wall and the septum free. Moderate arteriosclerosis of the aorta. In other organs no noteworthy findings.

In this case, with a large infarction of the posterior wall, a typical case record and a post-mortem verification, all the electrocardiographic changes, typical of coronary occlusion, have thus appeared strongly pronounced and then disappeared in the course

of 24 hours or perhaps during a still shorter lapse of time. If no second electrocardiogram had been taken until the day after the coronary occlusion, these changes would not have been observed. It would have seemed as if the patient's electrocardiogram had undergone no changes during his stay at the hospital, and we had had to register the case as a «silent» infarction.

In some textbooks on electrocardiography, as for example Scherf and Holzer and Polzer, it is indeed pointed out that the monophasic deformation of the electrocardiogram in cases of cardiac infarction is often exceedingly transient and may disappear within some hours. In such cases, however, the development of the typical coronary T wave can be observed if a series of electrocardiograms is taken, and the diagnosis thus even here electrocardiographically verified. This was impossible in the present case where the changes quickly disappeared, leaving the electrocardiogram mainly the same as before the attack — that is with a negative T_{III} wave but no typical coronary T wave. The electrocardiogram underwent no changes during the remainder of the observation time.

As to the importance of the time element, Hochrein in his monograph »Der Myocardinfarkt« only mentions the advisability of taking electrocardiograms every other or third day during the first three weeks in suspected cases of infarction in order to verify the diagnosis. He says further, referring to the so-called silent infarctions: »Wo trotz genauer elektrokardiografischer Kontrolle keine charakteristischen Veränderungen auftreten, muss eine Lokalisation des Infarktes in einer sog. «stummen Zone» (Morawitz und Hochrein) des Myokards angenommen werden. Es ist wahrscheinlich, dass diese «stummen Zonen» mit der Lokalisation der lateralen Infarkte übereinstimmen. Sichere Aufschlüsse bezüglich dieser Frage fehlen noch zur Zeit.« Such silent zones have been ascertained in dogs by Chavez and Mendez but as yet not in man; Coelho moreover doubts their existence. Hochrein mentions as another possible explanation: »Bei multiplen Infarkten ist natürlich eine gegenseitige Beeinflussung der elektrischen Erscheinungen möglich«, that is a seemingly normal electrocardiogram might be taken from a heart where the electrocardiographic changes, due to simultaneous infarctions of the anterior and posterior ventricular walls, cancel each other. Uhlenbruck tries to

explain the silent zone in a similar way in his monography «Die Klinik der Coronarerkrankungen», but does not attach any importance to the element of time. He discusses on the other hand several case reports, where it has not been possible to diagnose an infarction until several days after the illness has set in.

On account of the case here described, we want to stress the importance of early and often repeated electrocardiographic examinations, as the electrocardiographic changes due to infarction may disappear already within 24 hours after the attack has set in — at least in such cases where the electrocardiogram shows pathological changes, pointing to a coronary insufficiency already before the onset of the coronary occlusion.

Summary.

Description of a case of coronary thrombosis, verified at necropsy, (dorso-basal infarction), where an electrocardiographic examination had been made 1 ½ hour before the infarction set in and then several times during the next 24 hours. At the beginning of the infarction a typical, monophasic electrocardiogram was obtained, but already 24 hours later the electrocardiogram was quite similar to that taken before the coronary occlusion, and did not undergo any further changes during the patient's stay at the hospital.

In this connection the so-called «silent» electrocardiogram in cases of cardiac infarction is discussed, and the importance of early and repeated electrocardiographic examinations underlined.

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From the State Bacteriological Institute, Stockholm (Director: Prof. C. Kling) and the Statistical Institute of the University of Uppsala (Sweden). (Director: Prof. H. Wold).

A statistical note on Swedish epidemics of Poliomyelitis.

By

HERMAN WOLD.

(Submitted for publication July 12, 1943).

§ 1. In a series of very interesting investigations Mr Helge Petersen, Director of the State Meteorological Institute of Denmark, has made a theoretical and statistical analysis of the growth and decline of different types of epidemics (1, 2, 3, 4). A brief survey follows. Helge Petersen considers three types of epidemics: (a) the epidemic is caused and supported by infection from the outside (e. g. by infected food), not by individual contact; (b) the epidemic spreads by contagion; (c) the epidemics are caused by variations in the number of susceptible individuals. Petersen gives a mathematical theory of types a and b. In this analysis, he works out theoretical models of the development of the epidemics, the pertinent point of the construction being the alternative hypotheses concerning the manner of transmission of the disease; as further elements in the construction appear the number of inhabitants in the district considered, and the total number of individuals infected. In this way Helge Petersen arrives at theoretical frequency curves showing how the weekly number of new cases varies in the course of the epidemic. As corollaries of these results, he finds that the different types of epidemics are ruled by certain »laws», expressing general relations between the number

of inhabitants, the total number of infected people, and other elements of the theory.

The theoretical results can be directly compared with statistical observations on actual epidemics, and Helge Petersen performs a number of such tests. As to epidemics of type a, Petersen finds that in the simplest case of continued food infection the frequency curve should be an exponential curve. Combining this hypothesis with assumptions concerning individual variation of the incubation period, more complicated frequency curves of type a are derived, and he shows that such «compound» frequency curves fit the statistical records on certain *milkborne* epidemics of *Scarlatina*. — In his second type curve, which refers to epidemics spread by individual contact, we meet the «logistic» curve of Verhulst and Pearl. The logistic curve is shown nicely to fit observed frequency curves of *Influenza*, *Morbilli* and *Periussis*. Moreover, Helge Petersen shows that the following theoretical law deduced from the assumption of contagious infection is approximately fulfilled by the three diseases: For different epidemics of a certain disease in a certain town, the maximal weekly frequency of new cases varies in proportion to the square of the total number of cases in the epidemic.

Applying his second type curve to the statistics of *Poliomyelitis*, Helge Petersen finds that the logistic fits the observed frequency curves rather well, but it turns out that the above-mentioned law of contagious infection is not fulfilled. Concluding that the hypothesis of contagion does not apply to poliomyelitis, he looks for other regularities in the statistical records. Investigating poliomyelitis records from countries in various parts of the globe, and stating as a well-known fact that the higher the latitude, the shorter are the epidemic waves (see 4, p. 3518), Helge Petersen finds a more precise relation: As the latitude (φ) increases, the dispersion of the frequency curve (μ) — calculated as an average from several epidemics in the same district — decreases in proportion to the decrease of *sun radiation*.

As to latitudes between $\varphi = 25^\circ$ and $\varphi = 65^\circ$, sun radiation decreases steeply and almost linearly, and here the radiation curve fits strikingly well to Helge Petersen's observations of the dispersion μ .

Commenting on his statistical findings concerning poliomyelitis, Helge Petersen seeks for an explanation covering such features as

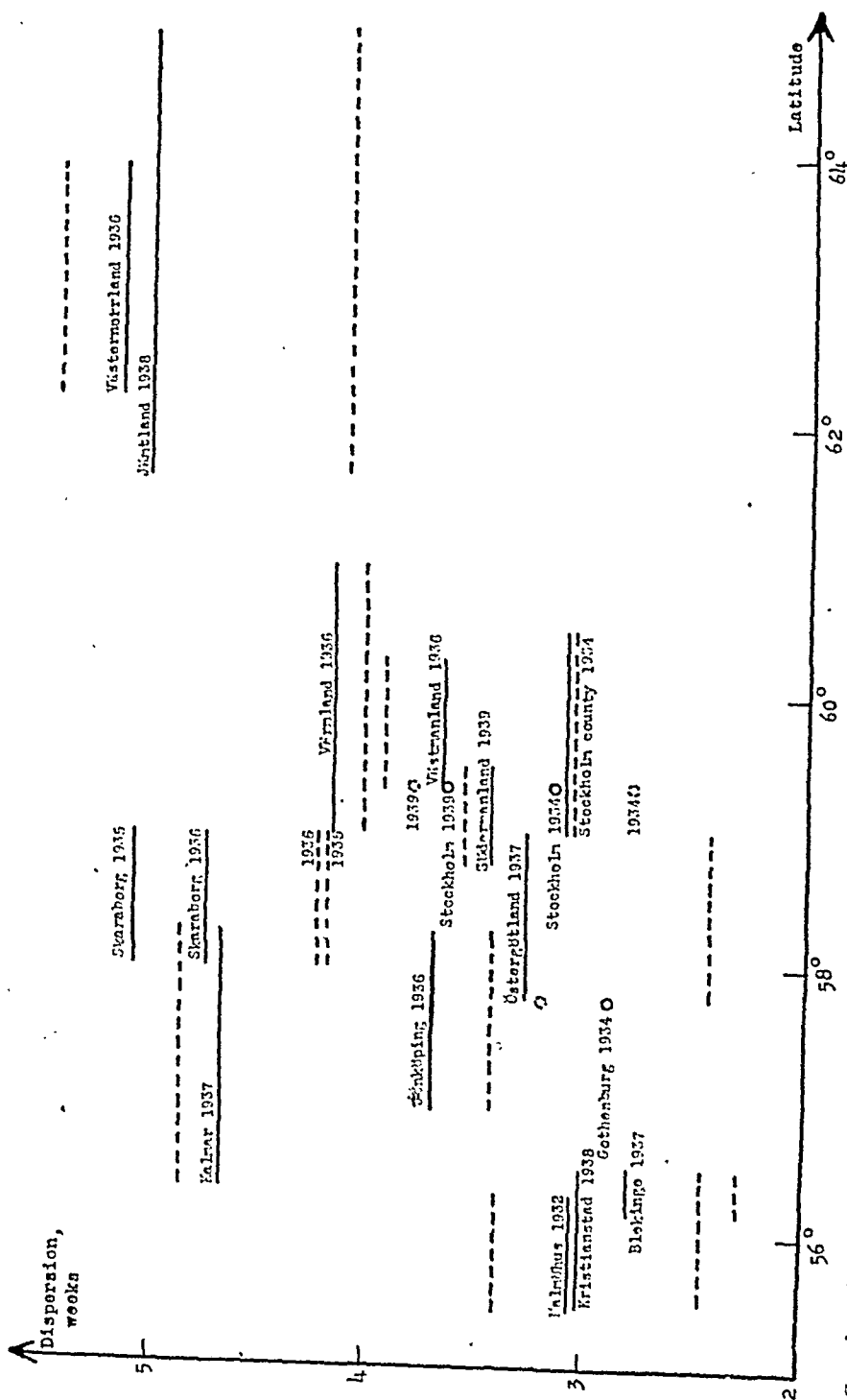
the geographical variation of μ and the well-known seasonal variation of the disease. He suggests the interpretation that the epidemic is of type c; more precisely, he suggests that the virus is present ubiquitously, that the epidemics are caused mainly by temporal variation in the resistance against infection, and that this variation is a direct or indirect effect of the geographical and seasonal variation of *sunshine*.

§ 2. As described by G. Olin and N. O. Heinertz (5), a detailed statistical material concerning poliomyelitis in Sweden 1930—39 has been collected in the State Bacteriological Institute, Stockholm. The material distinguishes between »paretic» and »abortive» cases, the former being cases with distinct symptoms of paralysis, the latter being the remaining, more or less vague cases. While the material is practically accurate and complete as to the paretic cases, it cannot be so for the abortive cases, the diagnosis here being difficult, and presumably varying according as an epidemic is or is not going on.

This material should be sufficient for testing whether Helge Petersen's relation between the latitude and the dispersion of the frequency curve of a poliomyelitis epidemic holds good for Sweden. In fact, the 24 counties of Sweden range between 56° and 63°, which according to Petersen's graphs should correspond to a variation of 1 week in the dispersion of the frequency curve¹; further, the material covers a considerable number of poliomyelitis epidemics scattered over the different counties of Sweden. Acting as a statistical consultee in the bacteriological institute, the present writer has arranged such a test. In this connection, I have profited from discussions with Professor C. Kling, Director of the State Bacteriological Institute, Dr. G. Olin at the same institute, and Professor G. Dahlberg, Head of the State Institute of Human Genetics and Race Biology, Uppsala. The numerical computations were made by Mr S. Malmquist, assistant to the Statistical Institute of Uppsala University. My sincere thanks are also due to Mr Helge Petersen for helpful criticism of the manuscript.

The test will now be briefly described. The statistical material of the Bacteriological Institute contains 8288 paretic cases. The

¹ Petersen claims explicitly that the dispersion is influenced not only by large (»macroscopic») but also small (»microscopic») variations in the latitude (see 4, p. 3520).



Graph. Dispersion of the frequency curves of 17 poliomyelitis epidemics in Sweden, plotted against the latitude range of the epidemic district.

classification is double, referring to (1) 24 counties and the cities of Stockholm and Gothenburg, and (2) the 24 half-month periods in the year. The details of the present calculation are as follows.

A. Only parietic cases have been taken into consideration.

B. In studying the tables for each county, all distinct epidemics have been noted. To decide when an epidemic starts and ends, a mechanical rule has been adopted in order to avoid subjective estimates: the epidemic starts when the fortnightly frequencies begin to increase steadily, and ends when they cease to decrease steadily. Any tail consisting of one or two fortnightly cases has been excluded.

C. In order to avoid epidemics which might be regarded as composed of two or more separate waves, only those epidemics have been taken into consideration for which the frequency curve is »smooth», more precisely, for which there is no exception from the steady increase (or decrease, respectively) in the fortnightly frequencies.

D. Among the epidemics thus defined, those have been excluded which do not comprise at least 50 cases. The material thus arrived at contains 17 epidemics.

E. For each of the 17 epidemics, the dispersion of the frequency curve has been calculated by the formula for the standard deviation; i. e. as the square root of the arithmetical mean of the squares of all deviations, deviations being measured from the arithmetical mean of the observations. The dispersion has been converted into weeks by counting each half-month as $2\frac{1}{7}$ weeks.

F. The accompanying graph shows the calculated dispersion, plotted against the latitude range of the county observed (unbroken lines).

§ 3. The graph gives no support to Helge Petersen's statement that the dispersion is negatively correlated with the latitude. On the contrary, if there is a connection, the correlation is positive. I have no intention to use the graph for a general criticism of Petersen's conclusions concerning poliomyelitis, but a few comments follow.

a. Thanks to their simple structure, Helge Petersen's theories of his two first type of epidemics (a and b) are very attractive, and it is remarkable indeed that he has found statistical records of scarlatina, influenza, morbilli and pertussis which are in agree-

ment with his theoretical results. This is the more interesting as the hypothetical basis of his analysis is simpler than other approaches discussed in the literature (thus, while Helge Petersen assumes that all persons susceptible to the disease will ultimately be infected in the course of the epidemic, Kermack and Mc Kendrick (6, 7, 8) have shown that there is a theoretical possibility that a contact epidemic may culminate and fade away before all susceptible persons have been infected).

It should be observed that Helge Petersen's theory of poliomyelitis is logically independent of his theories of the epidemics of types a and b, the chief argument being the «latitude relation», as we may call his statistical relation between the latitude and the dispersion of the frequency curve of poliomyelitis. Without expressing any opinion on his two first theories, it can be said that certain points in his poliomyelitis theory are questionable from medical and statistical viewpoints, as indicated below under γ and δ .

β . In computing the dispersion, say μ , Helge Petersen uses the short-cut formula

$$\mu = \frac{4}{10} \cdot \frac{n}{f_{\max}}$$

Here, n is the total number of cases in the epidemic, and f_{\max} is the maximal number of weekly cases; the formula is based on a simple estimate of the «steepness parameter» of the logistic curve, and on an approximative relation between this parameter and the dispersion of the logistic.

Applying also the short-cut formula to the present material, f_{\max} has been calculated simply as 7/15 of the maximal half-month frequency. The dispersions thus obtained are shown in the graph (broken lines). It is seen that the short-cut method gives rather large deviations from the ordinary method. However, the deviations are not systematic, and the short-cut values show, upon the whole, the same contrast with the findings of Helge Petersen.

The two sets of μ -values showing the same tendency, this observation agrees with a statement by Helge Petersen (3, 306) to the effect that different methods for computing the dispersion give the same result if the epidemic has a regular, symmetric course.

In his account of the numerical computations Helge Petersen

mentions (3, 303 f.) that n has been calculated as the number of cases occurring between the seasonal minima, and that f_{\max} has sometimes been obtained by graduation. Other points of difference are that the material of Helge Petersen is not confined to parietic cases, and that our test disregards all epidemics which are small or whose course is more or less irregular. Now, taking for granted that these differences are of secondary importance, our test has shown that there are exceptions from the latitude law.

γ. Helge Petersen's theory of poliomyelitis contrasts keenly to other approaches. We recall that C. Kling has presented arguments which suggest that poliomyelitis is one of those diseases where the infective matter is spread by intermediary hosts (9, 10). One of these arguments is that the geographical poliomyelitis distribution over the world is of a type which is different from the distribution of typical contact diseases, the poliomyelitis distribution being of the irregular type which is characteristic of *Typanosomiasis*, *Typhus icteroides* (yellow fever) and other diseases spread by intermediary hosts (cf. e. g. the maps in Manson's Tropical Diseases, 11). It should also be remarked that Helge Petersen's theory diverges from certain recent researches on poliomyelitis which point in the direction that the epidemics are caused by variation in either the virulence or the presence of the virus (see 12, also for other references).

We note that Helge Petersen's resistance theory agrees with the virus-host theory of Kling and others in refusing the contact theory. Now, as pointed out by S. Gard (13, p. 153—154), it is rather Helge Petersen's interpretation of his statistical findings than these findings themselves which stands in contrast to the virus-host theory. In fact, these findings are equally well compatible with the hypothesis of variations in the virulence of the virus or in the frequency of the intermediary host as with Helge Petersen's hypothesis of variation in the resistance against the disease.

δ. In view of the disagreement between the above graph and the latitude law, I have asked myself whether in proposing this law Helge Petersen has not fallen into one of the frequent pitfalls of «nonsense» correlation. This may possibly be the case if the latitude is related to one or more factors which are connected with the dispersion. Now, on inspecting Helge Petersen's table (4, p.

3520), it is seen that the districts with low latitude have a large population, Australia, Mississippi and New York being the extremes, while Iceland and Greenland with their small population figures occupy the other end of the table. Accordingly, if the dispersion of the frequency curve tends to be larger in larger and more populous districts — an assumption which seems to be plausible — this tendency is sufficient to explain at least a part of the correlation on which the latitude law is based. This remark is not decisive as to the validity of the latitude law, but it is safe to say that a special investigation of the possible effect of such factors as the size and the population density of the district must be made before the latitude law can be regarded as definitely established.

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Die Behandlung chronischer Polyarthrititis mit Adenosintri-phosphorsäure.

Von

BIRGER CARLSTRÖM und OLLE LÖVGREN.

(Bei der Redaktion am 2. Juli 1943 eingegangen).

In zwei vorhergehenden Mitteilungen (1 u. 2) berichteten wir über den therapeutischen Effekt teils bei verschiedenen rheumatischen Affektionen reiner Muskeladenylsäure (M. A.) und teils eines Präparats, das eine Mischung von M. A. und Adenosintri-phosphorsäure (A. T. P.) enthielt, und zeigten, dass bei gewissen Neuralgien und Myalgien wie Lumbago-Ischias, Myalgia dorsi, Diabetes-neuritis u. a. diese Präparate bei intravenöser Applikation einen deutlichen günstigen Effekt ergaben. Von 22 nach demselben Prinzip behandelten Fällen chronischer Polyarthrititis trat bei 18 eine wesentliche Besserung oder völlige Genesung ein, während 4 ganz unbeeinflusst blieben. Die Besserung, die darin bestand, dass spontane Schmerzen, Gelenkergüsse und Ödem ganz oder teilweise verschwanden, wobei sich auch das Bewegungsvermögen besserte, setzte schon nach einige Tage langer Behandlung ein und erreichte ihren Höhepunkt im allgemeinen nach 14 Tagen bis zu einem Monat. Die Nachteile dieser Behandlung lagen darin, dass die Präparate nur bei intravenöser Applikation eine deutliche Wirkung ergaben, und dass man dabei sehr vorsichtig zu Wege gehen musste, um Erscheinungen des Unbehagens in Form von Dyspnoe u. a. in unmittelbarem Anschluss an die Injektion zu vermeiden.

In der vorhergehenden Publikation (2) versprochen wir einen Bericht betreffs des Unterschiedes zwischen M. A. und A. T. P. in therapeutischer Beziehung. Wegen der Schwierigkeiten, A. T. P. in reiner Form darzustellen, wurden die fortgesetzten Untersuchungen wesentlich verzögert. Die chemische Natur der Adenosintriphosphorsäure bringt es mit sich, dass eine Kontrolle ihrer Zusammensetzung allein mit Hilfe chemischer Analyse auf grosse Schwierigkeiten stösst. Bei der Herstellung von A. T. P. war deshalb eine intime Zusammenarbeit zwischen Chemikern und Klinikern notwendig, und wir benutzen hier die Gelegenheit, der A. G. Astra und ihrem leitenden Chemiker Herrn B. Sjögren für die bei der Herstellung dieses Präparats aufgewandte mühevollen und wertvolle Arbeit unsern Dank auszusprechen.

A. T. P. wurde in reiner Form zum ersten Mal 1929 von Lohmann (3) und Fiske a. Subbarow (4) hergestellt, denen es gelang, die Substanz mit schlechter Ausbeute aus der Muskulatur zu isolieren. Das von uns jetzt angewandte Präparat enthält ungefähr 75 % A. T. P. Der Rest besteht aus Phosphaten sowie einem Teil Abbauprodukten, die aus der bei der Herstellung angewandten Hefe herkommen.

Bei der Herstellung von A. T. P. wurden verschiedene Methoden gebraucht. Die Endprodukte bei den verschiedenen Herstellungsmethoden ergeben bei chemischer Analyse, praktisch genommen, dasselbe Resultat, aber nur eins von denselben wirkt bei chronischer Polyarthritistherapie befriedigend. Es bedurfte vieler Zeit und Mühe, dieses Verhalten zu erforschen. Zur Zeit läuft eine diesbezügliche Untersuchung in Zusammenarbeit mit B. Sjögren, und das Ergebnis dieser Untersuchung wird später veröffentlicht werden.

Wir möchten doch schon jetzt hervorheben, dass der Effekt von A. T. P. demjenigen der Muskeladenylsäure bedeutend überlegen ist, was wir in mehreren Fällen in der Weise festzustellen vermochten, dass bei Polyarthritispatienten, die sich gegenüber der Behandlung mit M. A. als refraktär erwiesen, nach dem Übergang zu A. T. P. eine sehr schnelle Besserung eintrat. Hierzu kommt, dass A. T. P. auch bei intramuskulärer Applikation therapeutisch wirksam ist. M. A. ist, wie früher hervorgehoben, bei intramuskulärer Applikation praktisch genommen unwirksam, während A. T. P. bei beiden Applikationsarten fast den gleichen

Effekt hervorbringt. Zuweilen haben wir jedoch beobachtet, dass auch dieses letztere Präparat bei intravenöser Injektion wirksamer war als bei intramuskulärer.

Die Ursache des Verhaltens, dass M. A. bei intramuskulärer Applikation den grössten Teil ihrer therapeutischen Wirkung einbüsst, dürfte darin liegen, dass das Adenosin in der M. A. in der Muskulatur zu unwirksamen Inosin desaminiert wird, während in der A. T. P. die Pyrophosphatgruppe diese Umwandlung vermindert.

Alle im folgenden beschriebenen Fälle wurden schon von Anfang an nur mit A. T. P. behandelt. Allein in solchen Fällen, in denen während der A. T. P.-Behandlung eine Stagnation in der Besserung eintrat, versuchten wir ausserdem eine Zufuhr von Aneurin und Phospho-B-Vimin.¹ Eine weitere Besserung des Zustandes wurde hierdurch nicht festgestellt.

Die Dosierung der A. T. P. bestand täglich in 2 cm³ einer Lösung, die betreffs der Menge vorhandener A. T. P. mit einer 1-prozentigen Muskeladenylsäurelösung äquivalent ist. Während der letzten Zeit wurde die Dosis mitunter auf 3 cm³ derselben Lösung mit offenbar besserem Ergebnis erhöht.

Das weniger wirksame A. T. P.-Präparat, das im Anfang angewandt wurde, nennen wir im folgenden »A. T. P.-Lösung 1«, das später hergestellte, bedeutend wirksamere A. T. P.-Präparat bezeichnen wir »A. T. P.-Lösung 2«.

Sämtlichen Patienten wurde nach abgeschlossener Behandlung c:a 10 g Trockenhefe in Form von Fervin B täglich ordiniert.

Kasuistik,

Fälle mit normaler S. R.

Fall 1. ♀ 39 Jahre alt. Diagnose: Polyarthrititis subchronica. Anamnese. Pat. litt seit mehreren Jahren zeitweise unter Schmerzen und zeigte Schwellung der Fingergelenke und in der letzten Zeit auch der Fussgelenke. Während der letzten Monate hatten die Beschwerden zugenommen.

Aus dem Status vom 28. 12. 1942: S. R. 10 mm/Std. Afebril. Gelenke: Sämtliche Fingergelenke etwas angeschwollen. Pat. kann mit Schwierigkeit die Hände ballen. Fussgelenke: 0 obj. Sowohl Spontan- als auch Bewegungsschmerzen in den angegriffenen Gelenken. Pat. wurde 25mal mit 2

¹ Enthält 10 mg Aneurin und 4 mg Pyrophosphat pr cm³.

cm³ A. T. P.-Lösung 2 intramuskulär behandelt, und schon nach einigen Tagen Behandlung hatten die Spontanschmerzen nachgelassen. Nach abgeschlossener Behandlung, als die S. R. 5 mm/Std. betrug, hatte Pat. keine Spontanschmerzen, dagegen etwas Bewegungsschmerzen in den Fingergelenken. Gelenke 0 obj.

Fall 2. ♀ 22 Jahre alt. Wurde im Krankenhaus Mörby vom 7. 10. 1942 bis zum 26. 1. 1943 gepflegt. Diagnose: Polyarthrites chronica. Anamnese: Die Pat. war früher im grossen ganzen gesund gewesen, abgesehen davon, dass sie während der Zeit vom 3. 6. bis zum 8. 7. 1942 im hiesigen Krankenhaus unter der Diagnose Polyarthrites acuta gepflegt wurde. Sie war danach frei von Beschwerden bis Anfang Oktober, zu welcher Zeit Schmerzen und Anschwellung in den Fussgelenken sowie auch im linken Kniegelenk auftraten.

Aus dem Aufnahmestatus: S. R. 17 mm/Std. Afebril. Gelenke: Fussgelenke diffus geschwollen und palpationsempfindlich. Linkes Kniegelenk 0 obj. Spontan- und Bewegungsschmerzen in den angegriffenen Gelenken. Am 24. 10. wurde die Behandlung mit 2 cm³ A. T. P.-Lösung 2 täglich intramuskulär eingeleitet. Schon nach einige Tage langer Behandlung besserten sich die Spontanschmerzen. Am 1. 12. ist Pat. frei von allen Schmerzen, aber eine geringe Anschwellung in den Fussgelenken ist zurückgeblieben. Wegen dieser Schwellung verbleibt Pat. im Krankenhaus zur weiteren Behandlung. Bei der Entlassung am 16. 1. 1943 findet sich jedoch fortgesetzt eine unbedeutende Schwellung über den lateralen Malleolen. Keinerlei Schmerzen in den Gelenken. S. R. 10 mm/Std.

Fälle mit mässig erhöhter S. R.

Fall 3. ♂ 30 Jahre alt. Diagnose: Polyarthrites subchronica. Anamnese: Seit Frühjahr 1942 Beschwerden im Kreuz sowie Schmerzen im linken Knie- und linken Fussgelenk. Wurde im Herbst 1942 im Zentrallazarett in Västerås gepflegt, wo Pat. u. a. mit Röntgen behandelt wurde. Wurde in gebessertem Zustande entlassen. Im August 1942 trat eine Verschlimmerung ein mit Schmerzen im Kreuz und in den Leisten, ferner Beschwerden in den beiden Fussgelenken.

Aus dem Status vom 10. 9. 1942: S. R. 35 mm/Std. Afebril. Fussgelenke etwas geschwollen. Sowohl Spontan- als auch Bewegungsschmerzen in den angegriffenen Gelenken. Pat. wurde 23mal mit 2 cm³ A. T. P.-Lösung 2 behandelt, und zwar anfangs intramuskulär und später intravenös. Nach abgeschlossener Behandlung betrug S. R. 30 mm/Std. Fussgelenke 0 obj. Hüftgelenke: Fortgesetzt eine gewisse Bewegungseinschränkung. Keine Spontanschmerzen, aber etwas Bewegungsschmerzen. Bei einer Anfrage am 7. 1. 1943 war die S. R. 15 mm/Std. und Pat. teilte mit, dass er ganz frei von Beschwerden wäre und ohne Schwierigkeit seiner Arbeit nachgehen könnte. (Dauernd angestellter Feldwebel beim Flug).

Fall 4. ♂ 38 Jahre alt. Diagnose: Polyarthrites chronica. Im Jahre 1934 litt Pat. an unaufhörlichen Beschwerden in den Fussgelenken. 1940 und

1941 wurde Pat. teils in der Kuranstalt Nynäs und teils im Karolinischen Krankenhaus gegen chronischen Gelenkrheumatismus gepflegt. Pat. wurde in beiden Fällen mit Goldsalzinjektionen mit ziemlich gutem Ergebnis behandelt. Anfang des Jahres 1942 kehrten jedoch die Gelenkbeschwerden mit Schmerzen und Anschwellung des rechten Knie- und linken Handgelenks sowie der Fingergelenke wieder.

Aus dem Status vom 11. 12. 1942: S. R. 20 mm/Std. Afebril. Gelenke: Rechtes Kniegelenk etwas geschwollen und deformiert. Streckung ohne Besonderheiten. Kann bis zu ungefähr 70° beugen. Ausgesprochene Atrophie der Muskulatur des rechten Oberschenkels. Linkes Handgelenk etwas geschwollen. Kann die Hand bis ungefähr 10° dorsalflektieren. Sämtliche Fingergelenke etwas geschwollen. Während der Zeit vom 11. 12. bis zum 23. 12. 1942 wurde Pat. täglich mit 2 cm³ A. T. P.-Lösung 2 behandelt. Nach abgeschlossener Behandlung betrug die S. R. 20 mm/Std. Rechtes Kniegelenk Status quo. Die Atrophie der rechten Oberschenkelmuskulatur verblieb unverändert. Gelenke im übrigen 0 obj. Auf eine Anfrage am 10. 1. gibt Pat. an, dass der Zustand unverändert sei.

Fall 5. ♂ 28 Jahre alt. Diagnose: Polyarthrit. subchronica. Anamnese: Seit Anfang Juli 1942 Schmerzen in den Schulter-, Knie- und Fussgelenken. Unbedeutende Anschwellung, aber keine Rötung der angegriffenen Gelenke. Leichte subfebrile Temperatur. Am 4. 8. wurde die Tonsillektomie vorgenommen. Pat. wurde während der Zeit mit Acetylsalicylsäure mit vorübergehendem Effekt behandelt.

Status am 7. 9. 1942: S. R. 34 mm/Std. Afebril. Kniegelenke etwas geschwollen, freie Beweglichkeit. Fussgelenke unbedeutend geschwollen, freie Beweglichkeit. Sowohl Spontan- als auch Bewegungsschmerzen in diesen Gelenken. Täglich intramuskuläre Injektion von 2 cm³ A. T. P. Lösung I. Nach einige Tage langer Behandlung waren die Spontanschmerzen nach Angabe des Patienten verschwunden. Vom 28. 9. erhielt Pat. intravenöse Injektionen, wonach die Besserung schnellere Fortschritte machte. Am 9. 10. wurde die Behandlung abgeschlossen. Die S. R. betrug damals 11 mm/Std. Pat. hatte nicht die geringsten Schmerzen. Gelenke 0 obj. Auf Anfragen am 20. 12. 1942 und 11. 1. 1943 teilte Pat. mit, dass er fortgesetzt ganz frei von Beschwerden wäre und seine Arbeit ohne Schwierigkeit ausführte. (Dauernd angestellter Feldwebel beim Flug).

Fall 6. ♀ 28 Jahre alt. Diagnose: Polyarthrit. subchronica. Anamnese: Im Alter von 5 Jahren hatte Pat. rheumatisches Fieber. Sie soll im Anschluss an dasselbe einen Herzfehler bekommen haben. Pat. war frei von Beschwerden in den Gelenken bis zum Sommer 1942, als Schmerzen und eine geringere Schwellung in den Knie-, Hand- und Fussgelenken auftraten.

Status am 26. 10. 1942: S. R. 18 mm/Std. Cor: Rauhes systolisches Blasegeräusch. P. m. I₃ sin. Gelenke: Fussgelenke geschwollen, freie Beweglichkeit. Linkes Kniegelenk: Ein wenig geschwollen. Kann bis zu ungefähr 70° beugen. Spontan- und Bewegungsschmerzen in allen ange-

griffenen Gelenken. Pat. wurde nur während der Zeit vom 26. 10. bis zum 31. 10. täglich mit 2 cm³ A. T. P.-Lösung 2 behandelt. Nach abgeschlossener Behandlung waren die Schmerzen in den Gelenken verschwunden. Keine objektive Veränderung derselben wahrnehmbar. S. R. 10 mm/Std. Bei der Kontrolle am 11. 1. 1943 ist Pat. angeblich fortgesetzt frei von Beschwerden.

Fall 7. ♀ 36 Jahre alt. Pat. wurde im Krankenhaus Mörby während der Zeit vom 26. 9. bis zum 18. 11. 1942 unter der Diagnose Polyarthritis chronica gepflegt.

Anamnese: Seit einigen Jahren Gelenkbeschwerden mit Schwellung und Schmerzen in den Fingergelenken. Pat. wurde mehrmals poliklinisch mit Aneurin und Phospho-B-Vimin mit im allgemeinen guter Wirkung behandelt. Im August 1942 Verschlimmerung mit Schmerzen in den Fuss- und Handgelenken sowie im rechten Schultergelenk. Dieses Mal liess sich nach der Aneurinbehandlung keine Besserung wahrnehmen.

Aus dem Aufnahmestatus: S. R. 35 mm/Std. Afebril. Gelenke: Schwellung sämtlicher Fingergelenke sowie des rechten Handgelenkes. Kann mit einiger Schwierigkeit die Hände ballen. Spontanschmerzen im rechten Schultergelenk. Bewegungsschmerzen in den Knie-, Hand- und Fingergelenken. Am 30. 9. Einleitung intravenöser Behandlung mit 2 cm³ A. T. P.-Lösung 1 täglich mit anfangs gutem Ergebnis. Die Spontanschmerzen verschwanden und die Bewegungsschmerzen nahmen ab. Nach einiger Zeit hörte die Besserung auf und die S. R. hielt sich um 20 mm/Std. konstant, weshalb die Behandlung gegen A. T. P.-Lösung 2 in der gleichen Dosierung ausgetauscht wurde. Bei der Entlassung betrug die S. R. 6 mm/Std. und Pat. war ganz frei von Beschwerden. Gelenke 0 obj. Bei der Kontrolluntersuchung am 7. 1. 1943 ist Pat. fortgesetzt ganz frei von Beschwerden und erledigt seine Arbeit ohne Schwierigkeit (Krankenpflegerhilfe).

Fall 8. ♀ 65 Jahre alt. Pat. wurde im Krankenhaus in Mörby vom 26. 8. bis zum 18. 11. 1942 unter der Diagnose Polyarthritis chronica gepflegt. Anamnese: Seit dem Alter von 40 Jahren Gelenkbeschwerden, die anfangs in den Schulter-, Hand- und Fingergelenken auftraten. Pat. wurde wegen der Gelenkbeschwerden in mehreren Krankenhäusern gepflegt. In der letzten Zeit trat Verschlimmerung mit gesteigerten Schmerzen besonders in den Knie- und Fingergelenken ein.

Aus dem Aufnahmestatus: S. R. 22 mm/Std. Keine Temperatursteigerung. Gelenke: Sämtliche Fingergelenke sind geschwollen und deformiert und die Finger stehen in Ulnardeviation. Kniegelenke geschwollen und deformiert. Empfindlichkeit bei der Palpation. Kann diese Gelenke bis zu 90° beugen und in völliger Streckung bleiben 15°—20° übrig. In beiden Schultergelenken, besonders im rechten, beeinträchtigte Beweglichkeit. Pat. vermag die Hände nicht auf den Nacken zu legen. Spontanschmerzen in den Kniegelenken und ausgesprochene Bewegungsschmerzen in sämtlichen obengenannten Gelenken. Pat. wurde anfangs mit Aneurin und Phospho-B-Vimin ohne jede Wirkung behandelt.

wurde die intramuskuläre Behandlung von 2 cm³ A. T. P.-Lösung 1 täglich eingeleitet, und schon nach einigen Tagen gab Pat. an, dass sich die Spontanschmerzen in den Kniegelenken wesentlich gebessert hätten, während die Bewegungsschmerzen noch vorhanden waren. Am 5. und 6. Oktober trat eine Verschlimmerung ein, weshalb die Behandlung gegen 2 cm³ A. T. P.-Lösung 2 ausgetauscht wurde, wonach die Bewegungsschmerzen abnahmen. Bei der Entlassung betrug die S. R. 23 mm/Std. Gelenke: Pat. kann nunmehr die Hände zum Nacken führen. Kniegelenke: gutes Beugungsvermögen. In voller Streckung bleibt ein Rest von 10° übrig. Fingergelenke: Unveränderter Status. Keine Spontanschmerzen. Unbedeutende Bewegungsschmerzen in den Kniegelenken. Auf eine Anfrage am 20. 1. 1943 teilt Pat. mit, dass ihr Zustand unverändert sei.

Fall 9. ♀ 54 Jahre alt. Pat. wurde im Krankenhaus Mörby vom 22. 9. bis zum 16. 12. 1942 unter der Diagnose Polyarthritidis chronica gepflegt. Anamnese: Am 22. 12. 1942 fiel Pat. einem schwereren Schädeltrauma anheim. Sie wurde zunächst der chirurgischen Abteilung des Serafimer-lazarets eingeliefert und dann dessen neurologischer Abteilung überwiesen. Die vollständige Nervenuntersuchung u. a. durch Encephalogramm ergab ein negatives Resultat. Während des Aufenthaltes im Krankenhaus traten Schmerzen in den Finger-, Hand- und Schultergelenken meistens auf der rechten Seite auf. Pat. wurde der Kuranstalt Nynäs überwiesen, wo sie 2 ½ Monat lang unter der Diagnose Polyarthritidis chronica gepflegt wurde. Sie wurde mit Neosolganal ohne den geringsten Effekt behandelt. Da Pat. Anzeichen von Psychose zeigte, wurde sie ins Pflegeheim Ulv-sunda überführt. Bei ihrer Entlassung von dort fanden sich die Gelenkbeschwerden unverändert vor, weshalb Pat. ins Krankenhaus Mörby aufgenommen wurde.

Aus dem Aufnahmestatus: S. R. 25 mm/Std. Keine Temperatursteigerung. Gelenke: Sämtliche Finger in Beugekontrakturstellung mit ungefähr 20° Beweglichkeit in den Interphalangeal- und Metakarpalgelenken. Schwellung dieser Gelenke. Rechtes Schultergelenk: Pat. vermag den Arm ungefähr bis zu 20° zu heben, im übrigen vollständige Bewegungseinschränkung. Spontanschmerzen in den oben genannten Gelenken. Am 25. 9. wurde die Behandlung mit 2 cm³ A. T. P.-Lösung 1 täglich intramuskulär eingeleitet. Da sich der Zustand der Pat. nach 6 Tagen nur unbedeutend gebessert hatte, wurde die Behandlung gegen A. T. P.-Lösung 2 in der gleichen Dosierung ausgetauscht, wonach die Besserung etwas schnellere Fortschritte machte. Am 16. 11. gab Pat. an, dass die Spontanschmerzen ganz verschwunden wären, und dass sie im rechten Schultergelenk viel beweglicher sei. Bei der Entlassung betrug die S. R. 17 mm/Std. Weder Spontan- noch Bewegungsschmerzen vorhanden. Pat. kann die rechte Hand ohne Schwierigkeit zur Horizontalebene und mit einiger Schwierigkeit zum Nacken erheben. In allen Interphalangealgelenken freie Beweglichkeit. Keine Schwellung derselben, dagegen Schwellung sämtlicher Metakarpophalangealgelenke besonders auf der rechten Seite. In diesen Gelenken beschränkte Beweglichkeit, weshalb Pat. die Hände nicht zu ballen vermag.

Bei einer Anfrage am 7. 1. 1943 teilt Pat. mit, dass ihr Zustand unverändert sei.

Fall 10. ♀ 31 Jahre alt. Pat. wurde im Krankenhaus Mörby vom 7. 10. bis zum 7. 11. 1942 unter der Diagnose Polyarthritis chronica gepflegt.

Anamnese: Mutter und Vater mit chronischem Gelenkrheumatismus behaftet. Ende Februar 1942 stellten sich bei der Pat. Schmerzen in den Fingergelenken und später auch in den Handgelenken ein. Keine Temperatursteigerung. Anfangs mit Salazopyrin zu Hause ohne Effekt behandelt. Pat. wurde in der hiesigen medizinischen Abteilung vom 28. 5. bis zum 27. 8. 1942 unter der Diagnose Polyarthritis subchronica, Hyperthyreosis, Hypofollikulinuria gepflegt. Wurde mit Estilbin und Follikulin mit anfangs guter Wirkung behandelt. Pat. teilt mit, dass die Gelenksbeschwerden in den Tagen vor der Menstruation und während derselben zunehmen. Im September 1942 verschlimmerten sich die Gelenksbeschwerden.

Aus dem Aufnahmestatus: S. R. 24 mm/Std. Subfebrile Temperatur. Gelenke: Beide Kniegelenke etwas geschwollen. Rechtes Kniegelenk etwas empfindlich. Bewegungsvermögen im rechten ohne Besonderheiten, im linken Streckungsdefekt 10°. Ellenbogengelenke etwas geschwollen. Das linke zeigte ungefähr Streckungsdefekt 10°. Handgelenke geschwollen, ebenso sämtliche Fingergelenke. Schwellung in den Metakarpophalangeal- und in den ersten Interphalangealgelenken am stärksten ausgeprägt. Spontan- und Bewegungsschmerzen in sämtlichen angegriffenen Gelenken. Am 9. 10. wurde die intramuskuläre Behandlung mit 2 cm² A. T. P.-Lösung 1 täglich eingeleitet. Im Anschluss an die ersten Injektionen nahmen die Gelenksbeschwerden zu, besserten sich aber dann etwas. Die Behandlung wurde jedoch am 16. 10. gegen A. T. P.-Lösung 2 in derselben Dosierung ausgetauscht, weil nur eine unbedeutende Besserung wahrzunehmen war. Nach einige Tage langer Behandlung mit diesem letzteren Präparat trat eine deutliche Besserung mit Abnahme der Spontan- und Bewegungsschmerzen ein. Vom 2. 11. erhielt Pat. intravenöse Injektionen des gleichen Präparats, wonach die Besserung schnellere Fortschritte machte. Bei der Entlassung betrug die S. R. 18 mm/Std. und die Spontan- wie auch Bewegungsschmerzen waren ganz verschwunden. Fingergelenke unbedeutend geschwollen. Gelenke im übrigen 0 obj. Bei der Kontrolluntersuchung am 17. 11. gab Pat. an, dass sie in den Gelenken ganz frei von Beschwerden sei, abgesehen davon, dass die Finger zuweilen eine unbedeutende Schwellung zeigten. Am 11. 1. kehrten die Beschwerden in den Fingergelenken wieder. S. R. 29 mm/Std.

Fall 11. ♀ 39 Jahre alt. Diagnose: Polyarthritis chronica. Anamnese: Vor ungefähr 20 Jahren litt Pat. an gastrischen Beschwerden. Diese sind jedoch nunmehr ganz verschwunden. Ende März 1942 stellten sich Gelenksbeschwerden ein mit Schwellung und Schmerzen in den Zehen-, Hand- und Fingergelenken. Anfangs subfebrile Temperatur. Wurde im Krankenhaus Mörby vom 11. 4. bis zum 20. 4. 1942 unter der Diagnose Polyarthritis acuta lev. gepflegt. Behandlung:

mit gutem Ergebnis. Die Besserung hielt jedoch nur einen Monat an. Pat. wurde dann poliklinisch mit Phospho-B-Vitamininjektionen mit gutem Resultat behandelt. Die Besserung verblieb aber nur einige Monate. Pat. hatte dann einige Zeit Albyltabletten genommen und dadurch die Schmerzen in den Finger- und Handgelenken zum Teil beseitigt. Anfang Oktober 1942 nahmen die Gelenkbeschwerden zu, die nun auf die Fingergelenke und das rechte Ellenbogengelenk lokalisiert waren.

Aus dem Status vom 27. 10. 1942: S. R. 20 mm/Std. Afebril. Sämtliche Fingergelenke geschwollen. Kapsel in diesen Gelenken etwas verdickt. Pat. konnte nicht die Hände ballen. Spontan- und Bewegungsschmerzen in den angegriffenen Gelenken. Einleitung intramuskulärer Behandlung von 2 cm³ A. T. P.-Lösung I täglich am 27. 10. Bereits nach einige Tage langer Behandlung, gibt Pat. an, dass eine Besserung eingetreten sei. Da sie jedoch noch nicht völlig wiederhergestellt war, wurde am 17. 11. die Behandlung mit A. T. P.-Lösung 2 in derselben Dosierung eingeleitet. Die Besserung machte nunmehr schnellere Fortschritte und am 11. 12. wurde die Behandlung abgeschlossen. Die S. R. betrug damals 22 mm/Std. Pat. hatte jetzt nicht die geringsten Spontan- oder Bewegungsschmerzen in ihren Gelenken. Keine Schwellung der Fingergelenke. Vermag die Hände mit guter Kraft zu ballen. Pat. war frei von Beschwerden bis Anfang Januar 1943, als Schmerzen und Schwellung im rechten Zeigefinger und Empfindlichkeit an den Füßen von neuem auftraten. Am 7. 1. betrug die S. R. 29 mm/Std. Sämtliche Gelenke im rechten Zeigefinger etwas geschwollen. Fuss- und Zehengelenke 0 obj. Pat. erhielt von jetzt ab eine tägliche intramuskuläre Behandlung mit 3 cm³ A. T. P.-Lösung 2, und schon nach einige Tage langer Behandlung war sie frei von Beschwerden.

Fälle mit stark erhöhter S. R.

Fall 12. ♂ 81 Jahre alt. Gepflegt im Krankenhaus Mörby vom 15. 10. bis zum 25. 11. 1942 unter der Diagnose Polyarthrititis chronica.

Anamnese: Seit der Weihnachtszeit 1941 allmählich zunehmende Gelenkbeschwerden, anfangs nur in den Fussgelenken. Später kamen Schmerzen in den Knie-, Schulter- und Fingergelenken hinzu.

Aus dem Aufnahmestatus: S. R. 54 mm/Std. Afebril. Gelenke: Sämtliche Fingergelenke etwas deformiert und unbedeutend geschwollen. Pat. vermag nicht die Hände zu ballen. In den Ellenbogengelenken gutes Beugevermögen, aber bis zur völligen Streckung verbleiben 10°–15°. Fussgelenke: Unbedeutende Schwellung über dem lateralen Malleolus. Kniegelenke: Keine Schwellung. Kann bis zu 60° beugen. Bewegungsschmerzen in beiden Kniegelenken. Am 17. 10. wurde mit der intramuskulären Behandlung von 2 cm³ A. T. P.-Lösung 1 täglich begonnen. Da sich der Zustand des Pat. durch diese Behandlung nicht besserte, wurde am 22. 10. die Behandlung mit A. T. P.-Lösung 2 in derselben Dosierung eingeleitet, wonach eine deutlich wahrnehmbare Besserung eintrat. Bei der Ent-

Anamnese: Seit Neujahr 1942 zunehmende Schmerzen in den Fuss-, Zehen- und Kniegelenken. Pat. hat seit April 1942 zu Bett gelegen, da sie sich wegen der Schmerzen und der Schwäche in den Beinen nicht auf dieselben habe stützen können. Im Juli traten Schmerzen und Schwellung im linken Sternoclaviculargelenk hinzu.

Aus dem Aufnahmestatus: S. R. 65 mm/Std. Subfebrile Temperatur. Gelenke: Linkes Sternoclaviculargelenk geschwollen und empfindlich. Sämtliche Fingergelenke der rechten Hand geschwollen und bei Druck sowie bei aktiver und passiver Bewegung empfindlich. Finger der linken Hand weniger geschwollen. Pat. vermag nicht die Hände zu ballen. Rechtes Kniegelenk stark geschwollen. Schmerzen bei der Berührung sowie bei passiver und aktiver Bewegung. Pat. kann bis 90° beugen und bis zu völliger Streckung verbleiben 20°—30°. Linkes Kniegelenk geschwollen. Weniger ausgesprochene Berührungsempfindlichkeit. Gutes Bewegungsvermögen. Beide Fussgelenke geschwollen. Hier ausgesprochene Berührungsempfindlichkeit und Schmerzen bei passiver, weniger bei aktiver Bewegung. Spontanschmerzen in den Kniegelenken und Bewegungsschmerzen in sämtlichen oben genannten Gelenken. Pat. wurde anfangs mit Aneurin und Phospho-B-Vimin behandelt, wobei die Schmerzen etwas nachliessen. Am 25. 9. wurde die intramuskuläre Behandlung mit 2 cm³ A. T. P.-Lösung I täglich eingeleitet, und schon nach einigen Tagen waren die Fingergelenke frei von Schwellung und im rechten Kniegelenk hatte sich die Schwellung deutlich vermindert. Am 13. 10. wird eine Verschlechterung während der letzten Tage vermerkt, weshalb die Behandlung gegen A. T. P.-Lösung 2 in der gleichen Dosierung ausgetauscht wird. Der Zustand besserte sich danach von neuem. Bei der Entlassung betrug die S. R. 24 mm/Std. Linkes Kniegelenk, Finger-, Fuss- und Zehengelenke 0 obj. Rechtes Kniegelenk unbedeutend geschwollen. Beugung ohne Anmerkung. Bis zu vollständiger Streckung verbleiben 5°—10°. Pat. geht mit Hilfe zweier Stöcke. Keine Spontanschmerzen. Unbedeutende Bewegungsschmerzen im rechten Kniegelenk. Am 19. 1. 1943 gibt Pat. an, dass sie von neuem Schmerzen in den Beinen bekommen habe.

Von den Patienten wurden in der Regel sowohl vor als auch nach der Behandlung Serienblutproben zur Bestimmung der Brenztraubensäure und Zitronensäure entnommen. Sämtliche Blutproben wurden am Krankenbett entnommen. Die erste Probe wurde bei nüchternem Magen um 9 Uhr entnommen, und unmittelbar darauf erhielt der Patient 1 g Glykose pro kg Körpergewicht, musste aber im übrigen fasten. Blutproben wurden dann 1, 2 und 3 Stunden nach der Glykosebelastung entnommen. In einigen Fällen wurden ähnliche Serienproben auch während der Behandlungszeit entnommen. Die Patienten wurden dann um 8

Table 1.

Fall Nr.	mg % Brenztraubensäure im Totalblut				mg % Zitronensäure im Totalblut			
	vor	nach der Belast. Stunden			vor	nach der Belast. Stunden		
		1	2	3		1	2	3
2 { Vor d. Beh.	0.72	1.41	1.57	1.20	1.05	1.03	1.17	0.97
2 { Nach d. »	0.74	0.97	0.97	0.92	—	1.50	1.60	1.60
7 { Vor d. »	0.68	0.91	0.68	0.89	1.49	1.32	1.29	—
7 { Nach d. »	0.87	1.35	1.20	0.79	1.97	1.93	1.37	—
11 { Vor d. »	0.89	0.81	—	0.83	0.90	0.88	0.61	0.79
11 { Nach d. »	0.93	0.93	0.84	0.80	1.50	1.50	1.42	1.34
12 { Vor d. »	—	1.10	1.24	1.16	1.40	1.30	1.21	1.15
12 { Nach d. »	1.00	0.90	1.26	0.95	2.20	1.90	1.55	1.70
13 { Vor d. »	0.97	1.49	1.59	0.95	0.54	0.77	1.07	—
13 { Nach d. »	—	1.26	1.12	0.90	1.31	1.27	1.31	0.90
0 ¹ { Vor d. Beh. ..	0.80	0.84	1.11	1.02	1.30	1.20	1.20	1.20
0 ¹ { Während d. Beh. ..	0.98	1.3	0.98	0.93	1.19	1.03	0.88	0.74
0 ¹ { Vor d. » ..	0.80	1.15	0.98	0.98	1.30	1.20	1.25	—
0 ¹ { Während d. » ..	1.01	1.11	0.75	0.74	1.12	0.80	1.04	1.00
Gesund	0.86	1.16	1.30	0.84	1.60	1.60	1.52	2.09

Uhr mit 3 cm³ der oben genannten »A. T. P.-Lösung 2« intramuskulär behandelt, und hiernach wurden Blutproben auf die oben beschriebene Weise entnommen. Im folgenden werden in Tabellenform einige Werte von Fällen geliefert, in denen wir die Untersuchung sowohl vor als auch nach der Behandlung durchführen konnten.

Wir wollen jetzt nicht auf eine nähere Erörterung der Ergebnisse der Blutuntersuchungen eingehen, sondern nur hervorheben, dass die Brenztraubensäurewerte bei Polyarthritiden auf verschiedene Weise Abweichungen vom Normalen zeigen. Betreffs der Zitronensäurewerte wurden unsere früheren Beobachtungen bestätigt, nämlich dass dieselben bei unbehandelten Polyarthritidenfällen niedrig sind, und dass sie nach abgeschlossener Behandlung eine wesentliche Steigerung zu normalen Werten und sogar über dieselben hinaus aufweisen. Eine einfache Behandlung scheint eine Zunahme der Brenztraubensäurewerte und eine gleichzeitige Verminderung der Zitronensäurewerte zu bewirken.

¹ Ist in die Kasuistik nicht aufgenommen.

Table 2.

Zusammenstellung der Ergebnisse der A. T. P.-Behandlung bei chronischer Polyarthrit.

	Anzahl	Deutl. Besserung während d. Observationszeit	S. R. nach d. Behandl.			zeitw. Besserung	S. R. nach d. Behandl.			Keine Besserung	S. R. nach d. Behandl.
			u	m	n		u	m	n		
Fälle mit normaler S. R.	1 (♀)	1	—	—	—	0				0	
Fälle mit mässig erhöhter S. R.	3 (♂)	3	1	1	1	0				0	
	7 (♀)	5 ¹	1	1	3	2	1	1		0	
Fälle mit stark erhöhter S. R.	4 (♂)	4		3	1	0				0	
	2 (♀)	2		1	1	0				0	
Summa	17	15				2					0

u = unverändert

m = wesentlich vermindert

n = normal

Wir berichteten über insgesamt 17 Fälle chronischer Polyarthrit und deren Behandlung mit A. T. P. (siehe Tabelle 2). Seit unserer letzten Publikation wurden zwar mehrere Patienten behandelt. Da die Herstellung eines annehmbaren Präparates aber nicht vor Ende September 1942 gelang, hielten wir es nicht für zweckmässig, über solche Fälle zu berichten, welche mit Präparaten behandelt wurden, deren Zusammensetzung unzuverlässig war. Nach diesem Zeitpunkt sind alle bis zum Schluss behandelten Fälle hier mitaufgeführt.

Die 17 Fälle verteilen sich auf 10 Frauen und 7 Männer. Das Resultat der Behandlung war bei beiden Geschlechtern ungefähr gleichartig, vielleicht mit der Ausnahme, dass Frauen im Klimakterium oder überhaupt Frauen, bei welchen man einen Zusammenhang zwischen dem Verlauf der Polyarthrit und Änderungen in der inneren Sekretion vermuten zu können glaubte, durch die Behandlung weniger beeinflussbar waren. Bei diesen lag auch eine grössere Neigung zu Rezidiven vor.

Sämtliche 17 Fälle besserten sich deutlich infolge der Behandlung. Die Besserung begann in der Regel schon nach einigen weni-

¹ betreffs 3 dieser Fälle war die Observationszeit zu kurz, um sich über die Rezidivneigung äussern zu können.

gen Tagen nach Einleitung der Behandlung einzutreten und machte dann während der nächsten Tage ziemlich rasche Fortschritte. In einigen wenigen Fällen bestand der erste Effekt in gesteigerten Beschwerden mit Zunahme der Schmerzen und Anschwellung der kranken Gelenke sowie auch in mässiger Temperaturerhöhung. Nach einigen Tagen liessen diese Symptome jedoch nach und die Besserung schritt fort wie in den übrigen Fällen.

Das erste und charakteristischste Resultat der Behandlung bestand in einem Nachlassen und Aufhören der Spontanschmerzen und ebenso der Palpationsempfindlichkeit rings um die Gelenke. Auch die Anschwellung verminderte sich sehr bald. In den frischen Fällen, in denen das Krankheitsbild nur diese primären Symptome umfasste, ging die Genesung somit schnell vonstatten. Die übrigen Erscheinungen, wie Deformierungen, Skelettentkalkungen und Muskelatrophien, die als Sekundärphänomene zu betrachten sein dürften, wurden nicht direkt von der Behandlung beeinflusst.

Unsere früheren Beobachtungen, dass die Besserung nach der Behandlung mit M. A. und A. T. P. oft mit einer Normalisierung der S. R. verbunden ist, wurden weiterhin bestätigt. Ebenso fanden wir, dass in denjenigen Fällen, in welchen die S. R. wesentlich gesunken oder zu normalen Werten zurückgegangen war, die Besserung während der Observationszeit bestehen blieb. Doch sei hervorgehoben, dass die Observationszeit betreffs dieser Fälle kurz war.

In unserm vorigen Bericht über die Behandlung rheumatischer Krankheitszustände mit M. A. und A. T. P. umfasst die Kasuistik hauptsächlich solche Fälle, die mit M. A. behandelt wurden. Wir hoben hervor, dass Fälle mit normaler und unbedeutend erhöhter S. R. im allgemeinen am besten und schnellsten beeinflusst wurden, während Fälle mit erheblich erhöhter S. R. sich seltener besserten. A. T. P. scheint auf diese letzteren Fälle bedeutend besser einzuwirken. Aus einem Vergleich zwischen den Tabellen 2 und 3 geht hervor, dass von 10 mit M. A. behandelten Fällen mit stark erhöhter S. R. nur 3 eine dauernde Besserung zeigten, während 4 eine zeitweilige Besserung aufwiesen und 3 ganz unbeeinflussbar waren. Bei der Behandlung mit A. T. P. zeigten dagegen sämtliche von 6 behandelten Fällen mit stark erhöhter S. R. eine deutliche Besserung.

Table 3.

Zusammenstellung früherer Ergebnisse der M.-A.- und A. T. P.-Behandlung¹ bei chronischer Polyarthrit.

	Anzahl	Deutl. Besserung während d. Observationszeit.	S. R. nach d. Behandl.			zeitw. Besserung	S. R. nach d. Behandl.			Keine Besserung	S. R. nach d. Behandl.		
			u	m	n		u	m	n		u	m	n
Fälle mit normaler S. R.	4 ♂	3	—	—	—	0	—	—	—	1	1	—	—
	2 ♀	2	—	—	—	0	—	—	—	0	—	—	—
Fälle mit mässig erhöhter S. R.	2 ♂	2	—	1	1	0	—	—	—	0	—	—	—
	4 ♀	3	—	3	—	1	1	—	—	0	—	—	—
Fälle mit stark erhöhter S. R.	2 ♂	1	—	—	1	1	1	—	—	0	—	—	—
	8 ♀	2	—	2	—	3	2	1	—	3	3	—	—
Summa	22	13				5				4			

u = unverändert

m = vermindert

n = normal

Aus der Kasuistik geht hervor, dass »A. T. P.-Lösung 2« eine wesentlich sichere und schneller eintretende therapeutische Wirkung ergab als »A. T. P.-Lösung I«. Wir wenden nunmehr auch ausschliesslich das vorher genannte Präparat an.

Der Umstand, dass sämtliche Patienten nach abgeschlossener A. T. P.-Behandlung während längerer Zeit Trockenhefe einnahmen, ist für die Vorbeuge von Rezidiven in einigen Fällen wahrscheinlich von Bedeutung gewesen und hat vielleicht bewirkt, dass die Besserung nach dem Aufenthalt im Krankenhaus in mehreren Fällen weitere Fortschritte machte. Trotzdem kommen Rezidive nicht selten vor. Diese werden jedoch durch noch eine Behandlung schnell beeinflusst.

In einer Reihe von Fällen trat nach einige Zeit langer Behandlung mit A. T. P. ein Stillstand in der Besserung ein. In solchen Fällen brachte eine Unterbrechung in der Behandlung oder eine intensive Hefemedikation deutlichen Nutzen. Erst während der allerletzten Zeit wurde diese Beobachtung von uns gemacht, die wir auf folgende Weise erklären möchten.

¹ = Publiert in Acta Med. Scand. Vol. CX, 230, (1942).

Früher wurde hervorgehoben, dass der therapeutische Effekt von M. A. und A. T. P. kaum auf andere Weise zu erklären ist, als dass diese Stoffe, die bei den enzymatischen Phosphorylierungsprozessen im Organismus wirksam sind, eine Steigerung des Kohlehydratstoffwechsels herbeiführen. Irgendeine andere sichere biologische Wirkung dieser Substanzen kennt man nicht. Für eine solche Erklärung der Wirkung der Adenylsäuren spricht auch das Resultat der Blutanalysen, die bei Polyarthritispatienten vor und nach der Behandlung gemacht wurden. Unter der Voraussetzung, dass diese Auffassung richtig ist, und dass die Wirkung der Adenylsäuren unter anderem in einer Steigerung des Kohlehydratstoffwechsels besteht, liesse sich denken, dass diese Zunahme im Kohlehydratstoffwechsel nach einige Zeit langer Behandlung allmählich eine Verarmung des Organismus an solchen Enzymen zur Folge haben könnte, die bei den verschiedenen Phasen des Kohlehydratabbaus wirksam sind. Unter solchen Umständen würde eine Pause in der Behandlung oder noch besser eine Zufuhr obengenannter Enzyme oder von Hefe, die reichlich Material für eine solche Enzyymbildung enthält, diese Schwierigkeit beheben können.

Es kann schliesslich von Interesse sein hervorzuheben, dass auch Polyarthritis bei Haustieren insbesondere bei Hunden, aber auch beim Rinde, mit A. T. P. mit Vorteil behandelt wurde.

Bei Hunden kommt eine Arthritisform vor, die sich fast mit der primärchronischen Polyarthritis des Menschen vergleichen lässt mit hauptsächlich Lokalisation auf die Kniegelenke und mit starker Lahmheit. Diese Fälle zeigten trotz Behandlung mit den vorher angewandten Behandlungsmethoden eine deutlich fortschreitende Tendenz. 6 solche Fälle wurden bislang mit A. T. P. behandelt, und bei 4 von diesen war die Lahmheit bereits nach ungefähr eine Woche langer Behandlung ganz verschwunden; bisher (zwischen 1 bis 3 Monaten nach der Behandlung) ist kein Rezidiv aufgetreten. Die übrigen 2 zeigten bei der Röntgenuntersuchung deutliche Anzeichen von Knorpeldestruktion in den Gelenken. Bei diesen scheint die Behandlung eine nur unbedeutende und vorübergehende Besserung herbeigeführt zu haben.

Beim Rinde kommt während des Puerperiums Polyarthritis mit Lokalisation auf die hinteren Extremitäten, vor allem auf die Sacroiliaca- und Hüftgelenke vor. 2 solche Fälle genasen nach ungefähr

10 Tage langer Behandlung mit A. T. P. (15 cm³ A. T. P.-Lösung 2) vollständig.

Diese Fälle sind unter anderem deswegen von Interesse, weil hier nicht davon die Rede sein kann, den Effekt als die Folge suggestiven Einflusses auf den Patienten zu erklären.

Zusammenfassung.

Die Verfasser liefern einen klinischen Bericht über 17 mit Adenosintriphosphorsäure (A. T. P.) behandelte Fälle chronischer Polyarthrit. Von diesen trat bei 15 eine deutliche Besserung oder Genesung und bei 2 eine zeitweilige Besserung ein. Der Effekt der A. T. P. war bedeutend besser als derjenige der Muskeladenylsäure (M. A.), was u. a. darin zum Ausdruck kam, dass sich schwere Fälle, die durch M. A. im allgemeinen nicht beeinflusst werden, nach der A. T. P.-Behandlung deutlich besserten. Nach Ansicht der Verfasser beruht dieses darauf, dass die M. A. im Organismus schneller zerfällt und dadurch ausser Wirkung gesetzt wird.

Der Effekt von A. T. P.-Präparaten, die auf verschiedene Weise hergestellt wurden, variierte bedeutend. Dieses Verhalten bildet den Gegenstand fortgesetzter Untersuchungen.

Litteratur.

1. Carlström, Lövgren u. Sjögren: Klin. Woch.schr. 20, 793, (1941). —
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A contribution to the knowledge of the mode of action of sulfathiazole in the organism and its relation to the reticulo-endothelial system.¹

By

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Ever since the year 1935, when Domagk discovered prontosil, the effect of this substance and its derivatives in the organism with regard to bacteria has formed the subject of extremely keen investigations.

Several authors believe that the sulfanilamide derivatives damage the bacteria, either by killing them directly by impeding their development, or by reducing their virulence so that the defense mechanisms of the body can definitely ward off the infection.

However, others are of the opinion that these substances act as a stimulant on the defense mechanisms of the body, inter alia, by producing an increased activity in the reticulo-endothelial system (r. e. s.).

Finally, a few authors contend that a combination takes place between the two above-mentioned modes of action.

According to Domagk (1935), the effect of the sulfanilamide derivatives, with regard to infections, consists in a direct attack on the bacteria which weakens them. They, accordingly, assist the defense mechanisms of the body in their struggle. Nevertheless,

¹ We wish to express our thanks to Astra, A/B, for kindly supplying us with sulfathiazole for our experiments.

these preparations do not exert any stimulating influence on the phagocytosis.

Numerous experiments have proved that the sulfanilamide derivatives have a retardative effect *in vitro*, as well as *in vivo*, on the growth of the bacteria. Thus, in a series of works, Bliss and Long (1937), Greey (1938), Colebrook and Kenny (1939) and Keefer and Rantz (1939) have ascertained the bacteriostatic effect of these preparations. According to Levaditi and Vaisman (1935), the bacteria develop in the organism by the formation of a capsule which protects them against the phagocytes of the body. Furthermore, they produce the toxins leukocidin and hemolysin, which attack the white and red blood corpuscles. The sulfanilamides prevent the bacteria from forming these capsules, while they, simultaneously, neutralize the effect of leukocidin and hemolysin. This would, accordingly, explain their share in the fight against the bacteria. However, experiments performed by Gross, Cooper and Lewis, in 1938, reveal the fallacy of this «anti-capsule theory». Moreover, these authors have not found any evidence of an anti-endotoxic effect of sulfanilamide, a fact which Levaditi and Vaisman, in their experiments in 1937, professed to have discovered in certain derivatives. On the other hand, they do confirm the above-mentioned French scientists' statement regarding bacterial toxicity.

Osgood's attempt, in 1938, to cultivate hemolytic streptococci in bone marrow, with and without sulfanilamide, revealed complete destruction of the medullary cells of the bone in the cultures free from sulfanilamide. Further, in cultures with hemolytic streptococci upon blood agar, with and without sulfanilamide, Osgood was able to show that the hemolysis was smaller in the substrates with sulfanilamide contents. These results should, likewise, indicate an antitoxic effect of the substance.

A number of authors point out that interference with the bacterial metabolism constitutes the main activity of the sulfanilamides. Thus, Melon, Locke and Shinn (1940) consider themselves to have proved, by a series of experiments *in vitro*, that the sulfanilamides, by decreasing the decomposition of H_2O_2 , formed at bacterial metabolism, would block a catalase effect, thereby retarding the growth of the bacteria.

Similarly, Frisk (1943), in one of the latest comprehensive works in this field, stresses the fact that the sulfanilamide preparations

interfere with the bacterial metabolism, causing bacterial stasis. For the bacteria are dependent on paraaminobenzene acid for their further development and the effect of the sulfanilamides is believed to be due to their taking the place of the acid, thus depriving the bacteria of this factor. (Woods and Fildes 1940).

This interpretation of the mode of action of the sulfanilamides is, at present, generally accepted.

The few investigations in existence, dealing with the question of whether the defense mechanisms of the body are activated by the sulfanilamide preparations, are extremely contradictory. Thus, a number of authors, viz. Keefer (1938), Hammerschmidt (1939), Keefer and Rantz (1939), Tunnicliff (1939), have demonstrated in experiments *in vitro* that the leukocytes phagocytize a considerably larger amount of bacteria when chemo-therapeutics are added. Tunnicliff's figure indicates 7.5 times greater phagocytosis. The great majority of authors emphasize the fact that the increased phagocytosis is merely due to the damaging effect of the sulfanilamide preparations on the bacteria which have, consequently, been more easily taken care of by the normally functioning phagocytes. Keefer (1938), Hammerschmidt (1939), Domagk (1940), and others, were able to prove that, in animals treated with pron-tosil, the focus of the infection was enveloped by a solid bank of leukocytes. If this bank was broken through, a new one rapidly formed. This did not take place in the control animals. Thus, the sulfanilamide gives rise to a considerable collection of leukocytes, but the phagocytosis in the individual cells does not increase.

The works related above deal only with the relation of the sulfanilamides to some of the defense mechanisms of the body, viz. the leukocytes. However, also the mode of reaction of the r. e. s. at chemotherapy has been submitted to investigation. These inquiries have presented extremely contradictory results. Thus Greey (1938) declares that a blockade of the r. e. s., or splenectomy, does not in any way influence the effect of the sulfanilamides. Mc. Intosh (1939) confirmed this statement. He was unable to ascertain any increase of the phagocytes in the spleen after inoculation of test animals with cocci and sulfonamide. Wolff (1938) and Wolff and Julius (1939) were in a position to show, by means of tissue culture experiments acc. to Carrel, that the connective tissue phagocytes took up less trypan blue when first blocked with trypaflavine, while an earlier

dose of sulfanilamide had not hindered the absorption of colour. Nevertheless, to judge from the pictures illustrating the work of these scientists, the result does not seem particularly convincing.

Contrary to the above-mentioned authors, Bosse (1936) disclosed the fact that mice with extirpated spleen, when infected with hemolytic streptococci of a high virulence, were not, as the control animals, cured by prontosil. This might, possibly, indicate the significance of the r. e. s. with regard to the effect of prontosil treatment. After a blockade of the whole of the r. e. s., Docxy (1938) failed to obtain any effect of a sulfanilamide therapy. Finklestone, Sayliss, Paine and Patrick (1937) found, by means of some interesting experiments, that sulfanilamide stimulates the r. e. s. However, they were unable to determine whether the quantity of phagocytizing cells increased, or whether already existing cells disclosed intensified phagocytosis. The test animals, viz. rabbits, were administered Indian ink intravenously. Laparotomy was performed 4 days afterwards with partial splenectomy. During the next 15 days, the animals were given sulfanilamide per os, and, then, Indian ink was again injected. 4 days later the animals were killed. The contents of phagocytes in the spleen with Indian ink was compared, before and after the treatment, a reduplication being ascertained at the latter examination.

Material and method.

In the present work, male as well as female guinea pigs have been employed. However, in the individual experiments, the animals have invariably been of the same sex. Their weight has amounted to approximately 150—250 g., with the exception of some experiments which have taken a longer time. In the latter instances, some of the guinea pigs have attained a weight of approximately 350 g.

Since the purpose of part of our experiments has been to find out whether sulfathiazole affects the cells of the reticulo-endothelial apparatus, we have, during a comparatively long time, injected sulfathiazole intraperitoneally (*exp. I*). The dose has been fixed at approximately 0.5 g/kg of body weight, i. e. 0.5 g of sulfathiazole solution (Astra) per injection. A group consisting of 3

animals was given 5 cm³ sulfathiazole for 15 days in 10 injections, the animals being killed 12 hours after the last injection. All the animals were killed by a stroke on the neck. According to Saxl and Donath (1927), an unbloody and speedy death is necessary, since, otherwise, the phagocytizing r. e. s. cells are drained. 4 days prior to the killing of the animals, 1 cm³ of a 2 %-solution of trypan blue was injected intraperitoneally. This colour substance, which is comparatively non-poisonous, is taken up in the r. e. s., causing the cells there to become exposed. 4 control animals were administered trypan blue only, in the same quantity, and were killed at an equally long time after the injection.

At autopsy, preparations from the liver, spleen, bone marrow, omentum, lung, kidney, accessory kidney, thyroidea, lymphatic gland and the skin were taken aside for further investigation. These preparations were all fixed in a Susa-solution. According to Pfuhl (1931), trypan blue granules are best fixed in this solution. The preparations were treated in the usual histological manner and stained with neutral red.

In a second experiment (*exp. 2*), 4 days after an intraperitoneal injection of 1.5 cm³ of a 2 %-solution of trypan blue, a test excision from the liver and the omentum was performed on 4 guinea pigs. 20 days later, when the trypan blue-solution could be expected to have been eliminated from the body, a solution of 0.5 cm³ of sulfathiazole (= 1 g sulfathiazole) was injected intraperitoneally daily for 10 days. On the 11th day of the sulfathiazole cure, the same quantity of trypan blue was again administered intraperitoneally, which was followed by another 3 sulfathiazole injections of 0.5 cm³. The animals were killed 12 hours after the last injection and the same organs were taken aside for further investigation as in the first experiment. For the sake of control, 3 guinea pigs were given only trypan blue, i. e. 2 injections of 1.5 cm³, intraperitoneally at intervals of 34 days between each injection.

In a third experiment (*exp. 3*), subcutaneous weals of sulfathiazole-solution was injected locally in 3 places in epilated abdominal skin on altogether 5 animals. The sulfathiazole injection was repeated 2 days later. Another 2 days afterwards, trypan blue was injected, also in the same places. The animals were killed 3 days later and the following organs were examined: the liver, spleen, omentum, thyroidea and the skin pieces corresponding to

the weals. Only trypan blue was injected in the epilated abdominal skin of 3 control animals.

In examining all the preparations, we have attempted to obtain a subjective conception of the quantity of trypan blue in the r. e. s. cells. The trypan blue granular contents are denoted from one to four +, according to the filling degree of the cells, the quantity of cells containing trypan blue also being taken into consideration. Each of us has performed two examinations at an interval of one month, both times without knowing the number of the preparation in order to decrease, as much as possible, the source of error invariably entailed in a subjective method. The final comparison of the results from the two examination occasions have shown good conformity. In the few cases where this has not been achieved, the preparations have again been studied in detail. Also, in comparing the valuation of the granular contents by the two examiners, great agreement has been found. In the estimation regard has been taken not so much to the quantity of cells as, particularly, to the granular contents of the individual cells.

Results.

The results of the experiments where a single dose of trypan blue was injected at the end of a lengthy sulfathiazole cure will be seen in Table 1, together with control tests. All the organs in the tables, with the exception of the thyroidea, accessory kidney, and the kidney, contain cells belonging to the r. e. s. set up by Aschoff (1924). Since the perivascular cells in the accessory kidney (Lubarsch, 1921) and certain interfollicular cells in the thyroidea (Williamson and Pearse, 1926, Borell and Holmgren, 1943) are said to be contained in this system, these organs have been included in the investigation. In order to acquire a conception of the elimination of trypan blue also the kidneys were subjected to an examination.

In the liver preparations (*exp. I*) of all the control animals, the v. Kupffer cells contain a quantity of trypan blue granules, equal to that of the test animals, while in the case of one particular control animal a greater amount is found. In the bone marrow and the thyroidea, which also contain a great amount of r. e. s. cells, a somewhat larger quantity of colour granules are discovered

Table 1.

The test animals have been administered a single dose of trypan blue after having, for some time, been subjected to injections of sulfathiazole. Only trypan blue has been injected in the control animals.

Test animals.

Guinea Pig no.	Liver	Omentum	Spleen	Lymphatic gland	Bone marrow	Skin	Thyroides	Kidney	Accessory kidney	Lung
1	++	+++	++	+	++	++	—	—	(+)	+
3	++	+++	+	—	++	++++	+	++	0	+
12	+	++	+	—	++	+	+	++	0	+
<i>Control animals.</i>										
5	++	+++	+	0	+++	—	+++	++	+	—
6	++	+	+	0	+	++++	+	+	0	0
8	++++	+++	++	+	++++	++	++++	+++	—	(+)
73	++	++	+	++	—	+	++	++	+	(+)

+ = trypan blue granules 0 = no colour granules — = organ lacking.

in the control animals than in corresponding organs in the test animals, i. e. in the bone marrow in 3 control animals, and in the thyroides in 2. No pronounced difference has been ascertainable in the macrophages of the omentum, nor in the granular deposit in the r. e. s. cells of the spleen, as between test and control animals. On the whole, the splenic preparations contain a pronouncedly slight amount of trypan blue-phagocytizing cells in all the animals. Preparations from the lymphatic gland, the accessory kidney and the lung disclose only an insignificant quantity of r. e. s. cells, which, throughout, contain very inconsiderable amounts of trypan blue. No difference is ascertainable as between the control animals and the test ones. The skin preparations reveal an accumulation of macrophages containing trypan blue at the hair capillaries, but, even in this instance, no difference was found as between test and control animals. Finally, as regards the kidney, in all the preparations, the cells in tubuli contorti I have contained from a moderate to a great amount of trypan blue granules. However, the quantity of these granules has not varied to any noteworthy extent among the different animals. (Table 1)

Table 2.

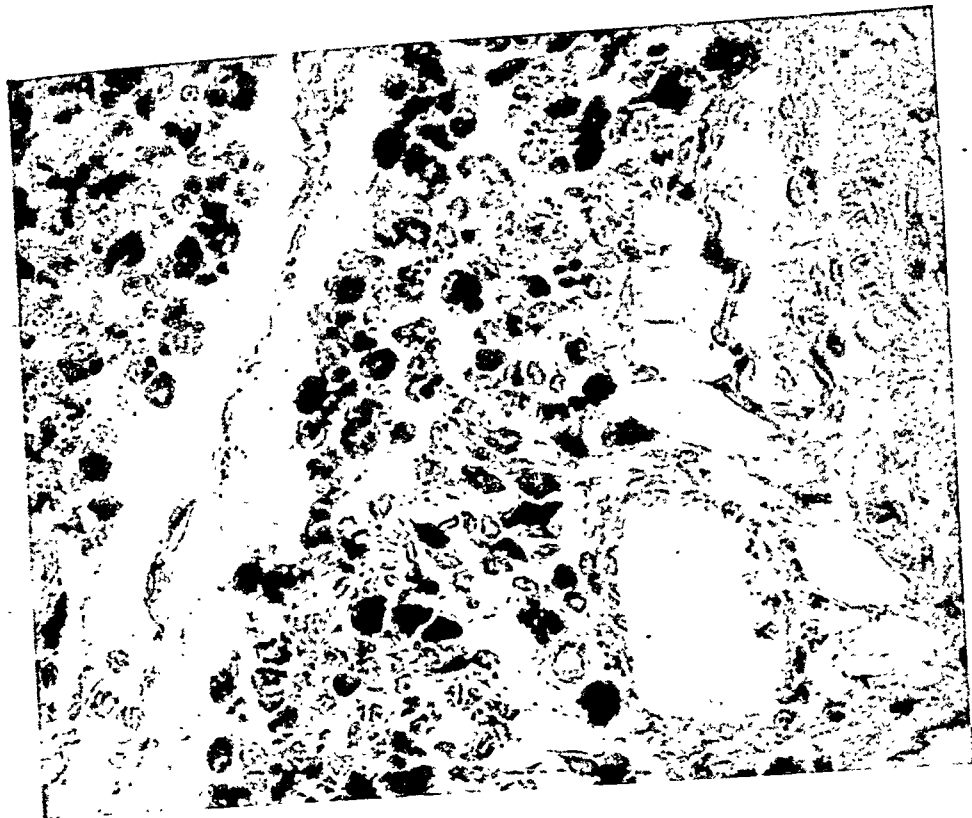
Guinea pigs from which a piece of liver and omentum were extirpated 4 days after an injection of trypan blue. The test animals were, then, injected with sulfathiazole for a long time. Both control and test animals were killed 4 days after a renewed injection of trypan blue.

Test animals.

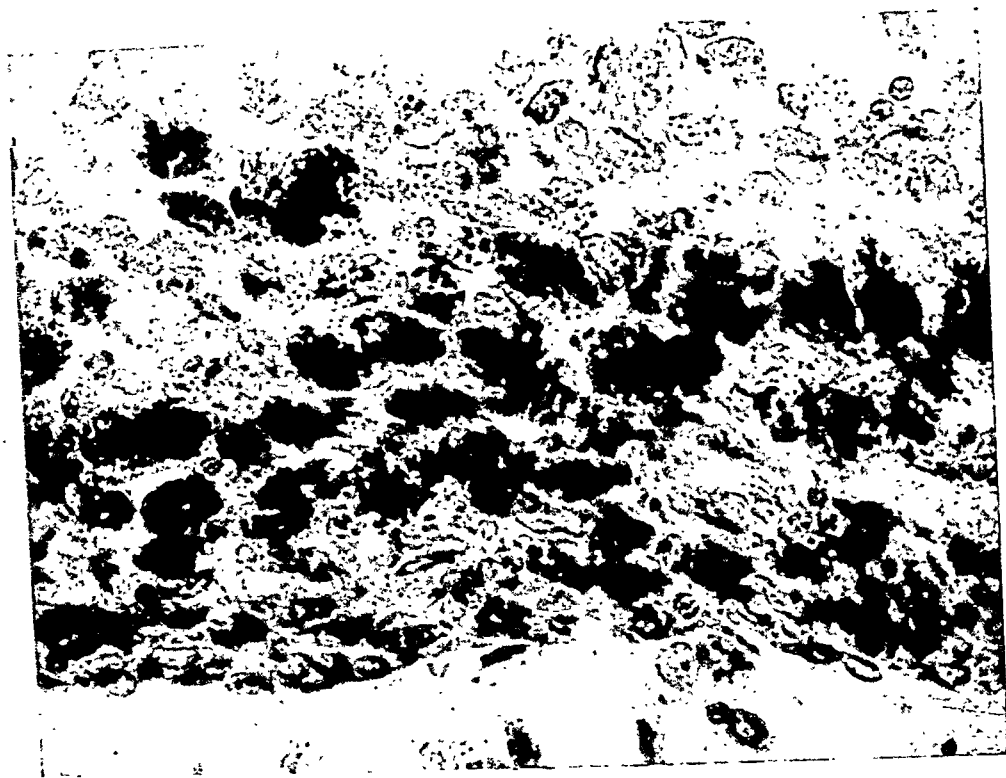
Guinea Pig no.	Liver, surgical preparations.	Liver Autoptical preparations.	Omentum. Surgical preparations.	Omentum. Autoptical preparations.	Spleen	Lymphatic gland.	Bone marrow.	Skin	Thyreoidea	Kidney	Accessory kidney	Lung
32	+	+	+	+++	(+)	+	+	++	(+)	+	0	0
56	++	++++	+++	++++	+++	+	(+)	+++	(+)	++	(+)	(+)
65	++++	+++	++	++++	(+)	(+)	(+)	+	+	0	0	(+)
67	+++	++++	++	++++	(+)	—	+	+	++	++	0	(+)
<i>Control animals.</i>												
69	+++	+++	++	++	(+)	—	—	+++	++	+	—	(+)
70	+++	+++	++	+++	+	(+)	+	++	+	++	(+)	+
71	+++	+++	+++	+++	+	+	(+)	++	+	++	(+)	(+)

+ = Trypan blue granules 0 = no colour granules — = organ lacking.

In order to find out whether phagocytosis in the same animals changes on account of a sulfathiazole dosage, the trypan blue content in *exp. 2* was examined in the v. Kupffer cells of the liver and the macrophages of the omentum, before and after the sulfathiazole dose (*Table 2*). From the table, it will be seen that the preparations from the liver contain a slightly greater amount of colour granules in two of the test animals, while the other two tend towards a slight decrease. In a comparison of the trypan blue content in operative and section preparations from the omentum, the latter appears to contain greater quantities in all the test animals. The preparations of the liver and the omentum from the control animals reveal, on the whole, the same content of trypan blue at operation, as well as autopsy (see *Fig. 1*). The other organs, subjected to examination, were found, principally, to hold the same amounts of colour in the control animals as well as the test ones. (see *Fig. 1—4*)



a



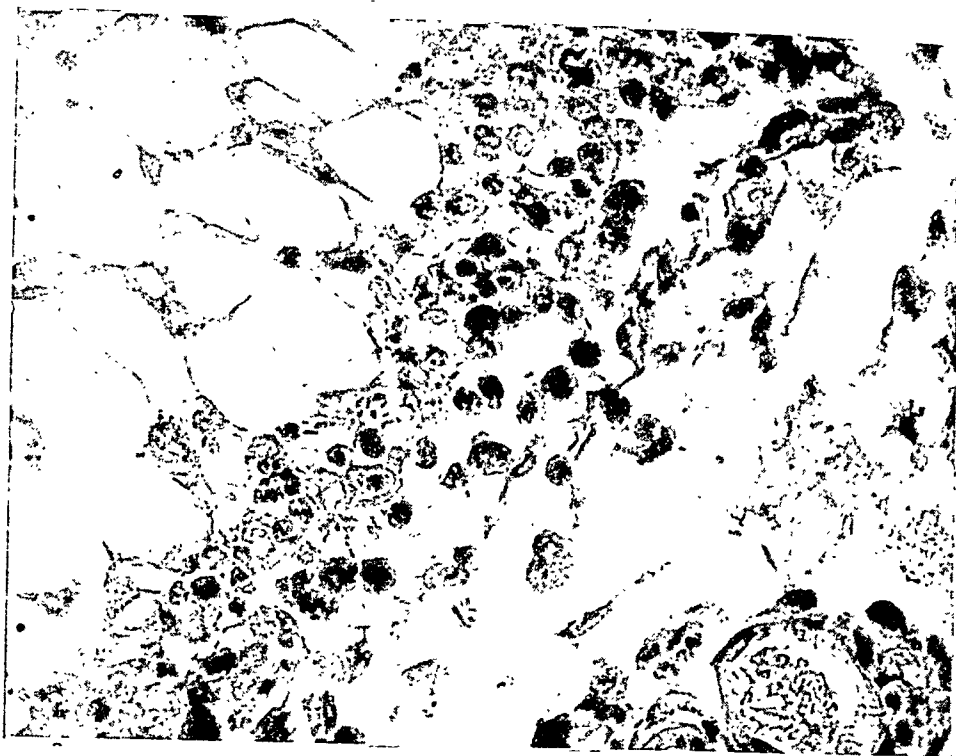
b

Fig. 1. Omentum from Guinea pig no. 56 (test animal).

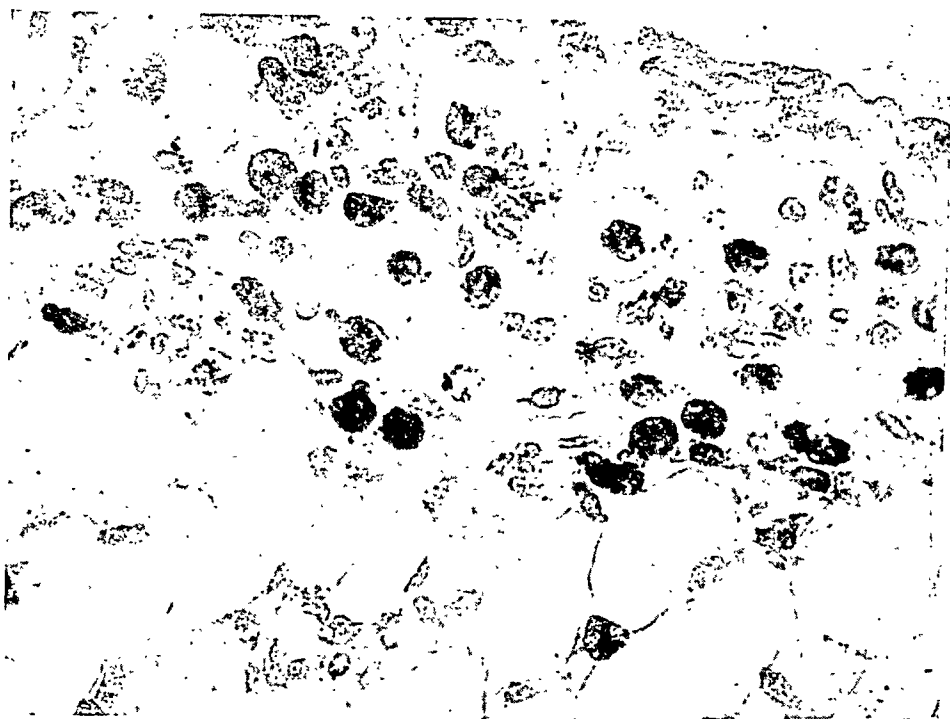
a) Surgical preparation, taken 4 days after the injection of a single dose of trypan blue. But a few colour granules in the connective tissue phagocytes.
 b) Autoptical preparation. After operation, the animal was for a long time treated with sulfathiazole intraperitoneally. Then another single dose of trypan blue was injected. The animal was killed 4 days later. The connective tissue phagocytes were well filled.

Section thickness: 5 μ .

Magnification: 600 times.



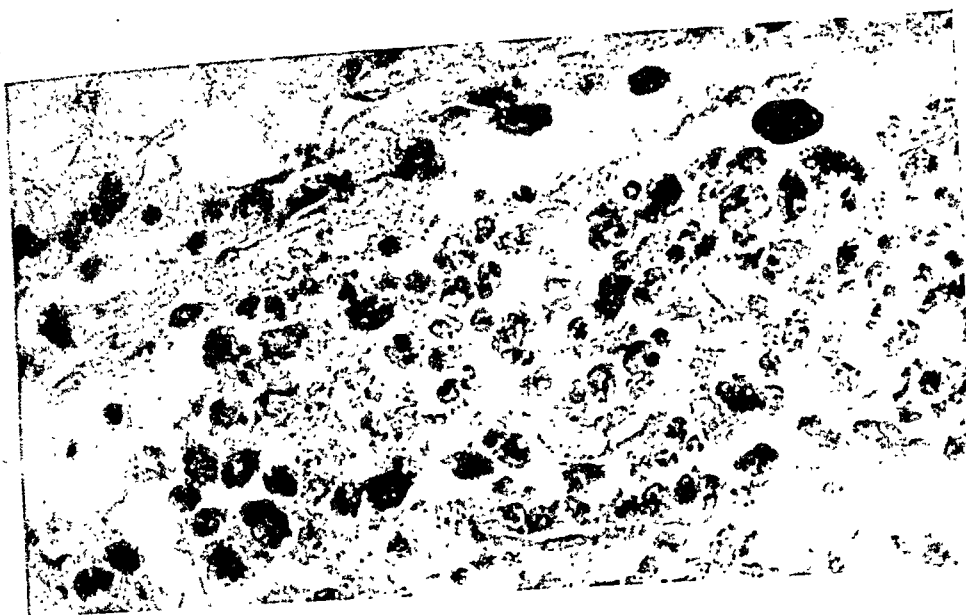
a



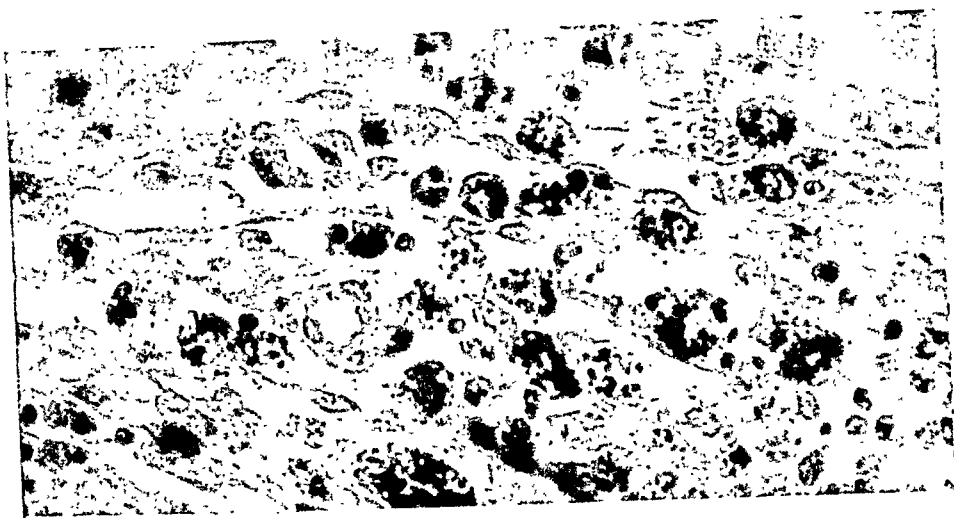
b

Fig. 2. Omentum from Guinea pig no. 67 (test animal). The animal was treated analogously to Guinea pig no. 56 (See Fig. 1.)

- a) Surgical preparation. The connective tissue phagocytes have taken up but a few trypan blue granules.
- b) Autoptical preparation. The connective tissue phagocytes well filled and strongly black-coloured.



a



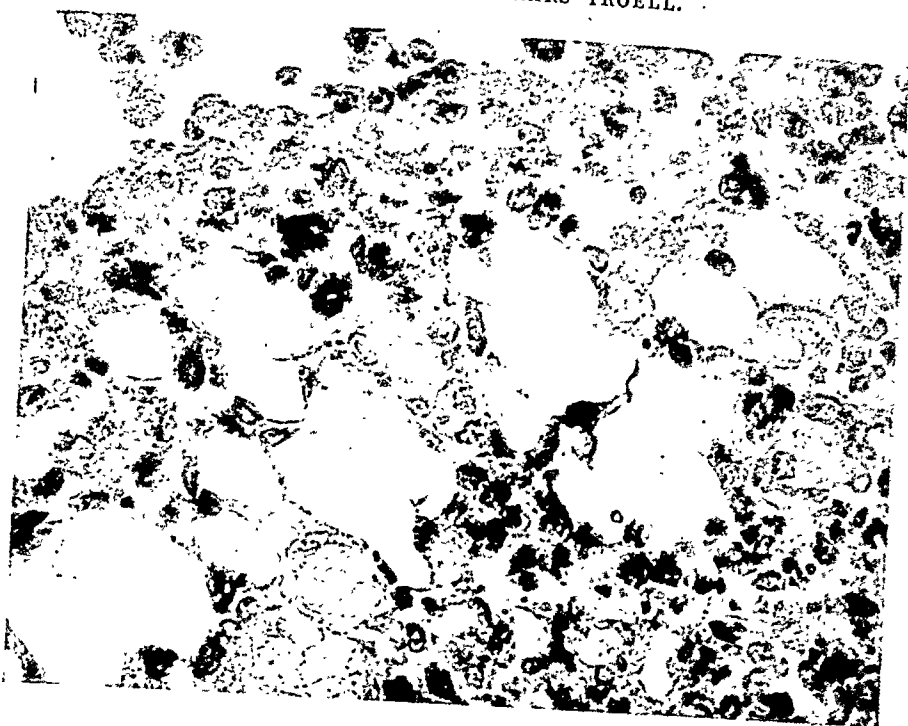
b

Fig. 3. Omentum from Guinea pig no. 69. (control animal).

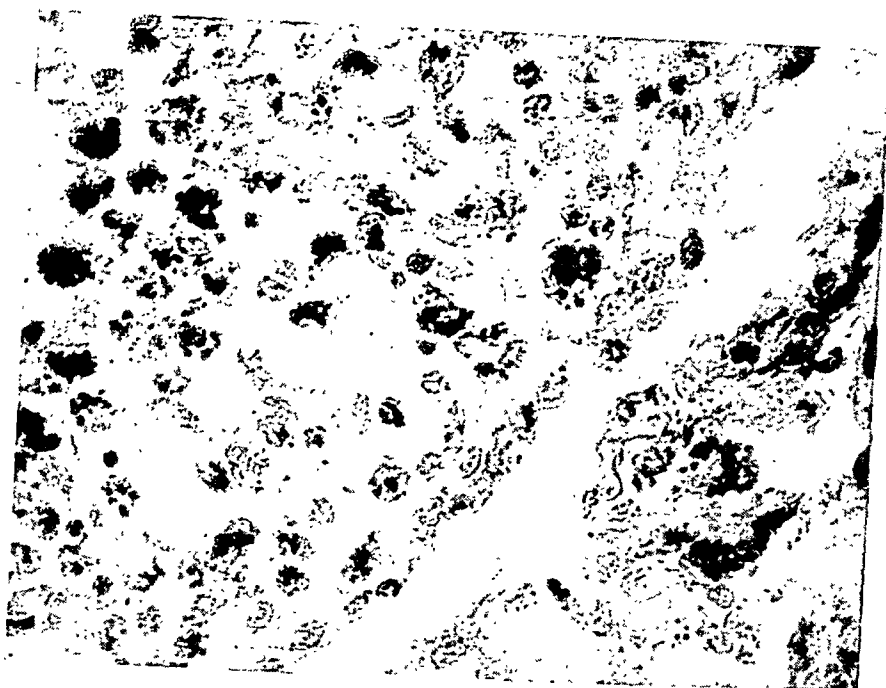
a) Surgical preparation, obtained 4 days after injection of a single dose of trypan blue.

b) Autoptical preparation. The animal was not treated with sulfathiazole between the first and second trypan blue injection, the latter having been administered after the same interval as in the case of the test animals.

The amount of colour granules stored in the phagocytes, on the whole, equal in a) and b).



a



b

Fig. 4. Omentum from Guinea pig no. 71. (control animal). The animal was treated analogously to Guinea pig no. 69.
a) Surgical preparation and b) autoptical preparation contained connective tissue phagocytes with approximately the same content of trypan blue granules

Table 3.

Weals of sulfathiazole have been injected in the test animals subcutaneously in the abdominal skin. Trypan blue was injected a few days later in the same places. Only trypan blue was administered to the control animals.

Test animals.

Guinea Pig no.	Skin piece I	Skin piece II	Skin piece III	Liver	Omentum	Spleen.	Thyroides
7	++	++	++	0	0	0	—
18	++	++	++	0	0	0	+
19	++	++	—	0	—	0	—
20	0	++	—	0	—	—	0
82	+	0	++	0	—	0	0
<i>Control animals.</i>							
21	+++	+++	+++	0	—	0	(+)
22	++	++	++	0	—	0	+
83	++	++	++	0	0	0	—

+ = Trypan blue granules 0 = no colour granules — = organ lacking

The results from *exp. 3* are collected in *Table 3*. By injecting sulfathiazole subcutaneously, we have attempted to occasion a strong local effect of this substance on the r. e. s. A comparison has later been made between the excised skin pieces from the test and control animals, the latter only being treated with trypan blue, in order to ascertain whether any difference existed in the granular amount. A possible decrease of this amount in the test animals might, then, be due, either to the fact that the sulfathiazole itself had been taken care of by the macrophages, causing a blockade of these cells, or speak in favour of the fact that sulfathiazole stimulated the phagocytosis capacity of the cells. *Table 3* disclosed a palpably greater amount of trypan blue granules in the macrophages of the skin pieces from one of the control animal than has been possible to observe in the preparations from the test animals. On the other hand, the two other control animals seem to have taken up, approximately, the same quantity of trypan blue as the test animals, which contained most colour gra-

nules in the phagocytizing cellular elements of the subcutis. The amount of colour which was injected into the animals has, apparently, been so slight that the resorbent quantities in the liver, the omentum and the spleen were not ascertainable. On the other hand, in three of the animals very small amounts of colour were observed in the interfollicular cells in the thyroidea.

Discussion.

As has already been pointed out in the introduction, according to the last years' observations, it appears definite that the sulfathiazole preparations hinder the normal metabolism of the bacteria, creating conditions which complicate their growth. Moreover, sulfanilamide and its derivatives are likely to influence the defense mechanisms of the body itself.

The purpose of the present investigation is to study the relation of sulfathiazole to the r. e. s. Even in earlier works (see page 589—590) the opinion is maintained that sulfanilamide preparations stimulate the phagocytosis capacity of the r. e. s. On the other hand, in the literature, authors, who undoubtedly constitute a majority, will be found, expressing the opinion that these preparations do not stimulate the phagocytosis, but only damage the bacteria, causing them to be more easily taken up into the r. e. s. If sulfathiazole directly influences the r. e. s., the substance in question may, either be assumed to be taken up by the cells in this system, which in this way decreases their capacity, or, on the other hand, actively stimulate them to increased phagocytosis.

Earlier works have disclosed that the function of the r. e. s. is influenced by substances phagocytized in it. Lepchne (1917—18) emphasized the fact that collargol injections hindered the storing of Fe and red blood corpuscles, while Elek (1924) was able to show that the injection of colloidal Fe produced a strong decrease of the bilirubin quantity in gall. According to Cannon, Baer, Sullivan and Webster (1929), a considerable decrease of the antibody formation occurred after repeated intravenous injections of Indian ink. In *exp. I*, when sulfathiazole was injected in large doses, the r. e. s. was likely to become blocked, if the substance was stored in this system. However, since the cells concerned, in test animals as well as control animals, contained approximately equal quanti-

ties of trypan blue granules, a blockade of the r. e. s. did not, apparently, take place. Only in some organs, i. e. the thyroidea and the bone marrow, do the cells of the test animals seem to contain less trypan blue. This would, possibly, indicate a blockade, but the difference as against the control animals is, however, so insignificant that definite conclusions cannot be drawn from our restricted experimental series. Moreover, since it is established that sulfathiazole is very rapidly eliminated from the body, and that approximately 80 %—90 % (Frisk, 1943) are found in the urine, the quantities which may, possibly, remain in the body are, no doubt, too slight to cause a blockade of the r. e. s.

Nor has any definite result been achieved in experiments with local blockade of the connective phagocytes of the subcutis. Kusnetzowsky (1923) and Katsunuma and Sumi (1924) declared that it is possible to attain such a blockade. When sulfathiazole is taken up by the phagocytes of the connective tissue, they should not, in the actual injection area, be capable of absorbing subsequent injections of trypan blue. From *Table 3* it will be seen that such an effect has not been obtained. Consequently, everything speaks in favour of the fact that, when sulfathiazole is taken up by the r. e. s., this occurs in but small quantities. This observation is in good conformity with that of Julius and Wolff (1939).

Our first experiment disclosed an, apparently, greatly varying capacity of the r. e. s. in the different animals and, further, great individual variations in the phagocytizing power of this system. Accordingly, we proceeded to compare the r. e. s. in each individual animal, before and after lengthy and strong sulfathiazole dose (see page 594). As will be seen from *Table 2*, all the omenta from the test animals were found to contain a palpably greater quantity of trypan blue granules after the lengthy and intense sulfathiazole treatment than before it. The control animals, on the other hand, seem to have, approximately, the same amount of colour in the omentum after the respective trypan blue injections. It is conceivable that the increase of the trypan blue granules in the omentum, after the sulfathiazole cure, is due to the fact that the macrophages still maintain some colour from the first trypan blue injection at the end of the experiment. Accordingly, with regard to the control animals, an increased trypan blue content should,

supposedly, be found in the autoptical preparations as compared with the surgical ones. However, no difference was discovered. This argues in favour of the fact that the 20 days, which elapsed between the operation and the beginning of the sulfathiazole cure, were sufficient for the organism to eliminate the colour substance. In the other organs, subjected to examination and containing r. e. s. cells, no palpable difference was observed. It should be noted that in the estimation, regard has only been taken to the amount of trypan blue granules within the different cells and not to the number of cells. This is due to the irregular distribution of the macrophages of the omentum, which appeared in accumulations separated by areas rich in fat. In some instances, only smaller parts of these macrophage accumulations have been included in the preparations. Consequently, these omenta would have been at a disadvantage if regard had been taken to the amount of cells containing colour. The fact that a difference has been found only in the phagocytizing power of the macrophages of the omentum may be explained by the intraperitoneal injection of sulfathiazole, which involved a considerably larger concentration of the substance in the peritoneal cavity than in the other parts of the organism. According to Frisk's investigation, as early as in the first 24 hours after the administration of sulfathiazole, great quantities of this substance were found in the urine (Frisk, 1940, 1943). During the following 48—72 hours so much was excreted, that altogether approximately 90 % disappeared via the urine during this time. Therefore, it appears probable that, in our experiments, only the last injections of sulfathiazole are of any significance in influencing the macrophages of the omentum.

Several authors (Keefer, Hammerschmidt, Keefer and Rantz, Tunnicliff, and others) have earlier showed that considerably larger amounts of bacteria are phagocytized after sulfanilamide treatment. However, they believe that this is occasioned by the fact that the substance directly damages the bacteria which are, then, more easily phagocytized. Since we have employed in our experiments trypan blue in order to disclose the phagocytizing power, an increase of this substance in the r. e. s. after sulfathiazole injections should, probably, be due to a stimulation of the phagocytosis. Our results point in the same direction as Finkelstone, Sayliss, Paine and Patrick's observations (see the History). They showed

that an increased number of cells phagocytized in the spleen after sulfanilamide treatment, but were unable to ascertain whether the phagocytosis of the individual cells had increased. Since we believe that we have found such an increase by means of our experiments, this must, in all probability, be due to the fact that we have administered a considerably greater dose and, in addition, distributed the substance intraperitoneally, while the above-mentioned authors had given sulfanilamide through the mouth.

Summary.

The mode of action of sulfathiazole has been subjected to an inquiry, and its relation to the reticulo-endothelial system has been examined. The investigation has offered the following results.

1. Large interated doses of sulfathiazole, which were administered intraperitoneally to guinea pigs, increase the amount of trypan blue granules in the macrophages of the omentum.

2. In other organs submitted to examination, belonging to the reticulo-endothelial system, i. e. the liver, spleen, bone marrow, lymphatic gland and thyroidea, sulfathiazole did not produce any palpable or uniform change in the quantity of absorbed colour.

3. Our results also serve to prove that sulfathiazole cannot «block» the reticulo-endothelial system when taken up into this system.

4. In addition to its capacity to interfere with the bacterial metabolism, sulfathiazole is, apparently, capable of stimulating, in a high concentration, the reticulo-endothelial system to increased phagocytosis.

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